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Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial

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ABSTRACT

OBJECTIVE
To estimate the effect of a moderate to high intensity aerobic and strength exercise training programme on cognitive impairment and other outcomes in people with mild to moderate dementia.

DESIGN
Multicentre, pragmatic, investigator masked, randomised controlled trial.

SETTING
National Health Service primary care, community and memory services, dementia research registers, and voluntary sector providers in 15 English regions.

PARTICIPANTS
494 people with dementia: 329 were assigned to an aerobic and strength exercise programme and 165 were assigned to usual care. Random allocation was 2:1 in favour of the exercise arm.

INTERVENTIONS
Usual care plus four months of supervised exercise and support for ongoing physical activity, or usual care only. Interventions were delivered in community gym facilities and NHS premises.

MAIN OUTCOME MEASURES
The primary outcome was score on the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) at 12 months. Secondary outcomes included activities of daily living, neuropsychiatric symptoms, health related quality of life, and carer quality of life and burden. Physical fitness (including the six minute walk test) was measured in the exercise arm during the intervention.

RESULTS
The average age of participants was 77 (SD 7.9) years and 301/494 (61%) were men. By 12 months the mean ADAS-cog score had increased to 25.2 (SD 12.3) in the exercise arm and 23.8 (SD 10.4) in the usual care arm (adjusted between group difference −1.4, 95% confidence interval −2.6 to −0.2, P=0.03). This indicates greater cognitive impairment in the exercise group, although the average difference is small and clinical relevance uncertain. No differences were found in secondary outcomes or preplanned subgroup analyses by dementia type (Alzheimer's disease or other), severity of cognitive impairment, sex, and mobility. Compliance with exercise was good. Over 65% of participants (214/329) attended more than three quarters of scheduled sessions. Six minute walking distance improved over six weeks (mean change 18.1 m, 95% confidence interval 11.6 m to 24.6 m).

CONCLUSION
A moderate to high intensity aerobic and strength exercise training programme does not slow cognitive impairment in people with mild to moderate dementia. The exercise training programme improved physical fitness, but there were no noticeable improvements in other clinical outcomes.

TRIAL REGISTRATION
Current Controlled Trials ISRCTN10416500.

Introduction

Nearly 47.5 million people worldwide have dementia.1 The challenge to families and health and social services is substantial.1 The hypothesis that aerobic and strengthening exercise might slow cognitive impairment in dementia has gained widespread popularity. Many studies describe plausible mechanisms using mammalian models, but there are fewer studies using human participants.2 3

The results of recent systematic reviews of trials of exercise training in people with dementia have conflicted. One review concluded that exercise can improve physical but not cognitive impairment, neuropsychiatric symptoms, or health related quality of life.4 Another suggested that aerobic exercise has a positive effect on cognitive impairment, regardless of the type of dementia or dose of intervention.5 All reviews confirm the multiplicity of small studies of low methodological quality, limited duration of follow-up, and high unexplained heterogeneity in findings. In 2012, the UK government launched a prime minister’s challenge in which research to seek a cure for, or alleviation of, dementia symptoms was set as a national priority. The National Institute for
Health Research (NIHR) commissioned the Dementia And Physical Activity (DAPA) trial to inform the debate about the potential benefit of exercise on cognitive impairment in people with dementia.

We compared the effect on cognitive impairment at 12 months of a combination of a moderate to high intensity aerobic and strength exercise training programme in addition to usual care compared with usual care alone in people with mild to moderate dementia. We designed and tested an intervention that targeted known mechanistic pathways in vascular and Alzheimer’s type dementia and which, if found effective, could be scaled for use within the UK National Health Service.

Methods

Study design

A full protocol has been published previously. This was a multicentre, pragmatic, investigator masked, randomised controlled trial. Random allocation was 2:1 in favour of the exercise arm. Participants were recruited from memory services in university and district general hospitals, NIHR dementia research registers and networks, and from primary care practices and community dementia services in 15 regions across England. Interventions were delivered in community gym facilities and occasionally in NHS facilities.

We recruited people with mild to moderate dementia and, when available, their primary carer. We asked carers to provide data about their relative or close friend with dementia for measures that specified the primary respondent should be the carer. For people with dementia, we determined capacity to consent in accordance with the principles of the Mental Capacity Act (2005) using research nurses and physiotherapists who received specific training. The assessment of capacity was based on a subjective opinion developed during the preliminary phases of enrolment. The nurses or physiotherapists made an assessment, using gentle questioning, to determine how much information was understood and processed. When people with dementia were assessed as having capacity, we obtained their informed consent. If people with dementia were assessed as lacking capacity, we asked the primary carer or personal consultant about the participant’s past and present wishes and feelings about taking part in research studies and we asked the primary carer or personal consultant if people with dementia were unable to give informed consent, and there was no carer or personal consultant, we sought nominated consultees who were well placed and prepared to act on behalf of potential participants (for example, a health professional independent of the study). We excluded people who lacked capacity and had no personal or nominated consultant. Carers gave their written informed consent to provide data about the person with dementia. We checked agreement for continued participation at each visit.

During the supervised period, people with dementia were overseen in groups of six to eight participants to minimise costs. In each group session, aerobic exercise consisted of static cycling with a five minute warm-up period followed by up to 25 minutes of moderate to hard intensity cycling, depending on tolerance level. We set target intensity using a six minute walk test according to Luxton10 and progressed the aerobic challenge using recognised methods.5 Strength training consisted of arm exercises using hand held dumb bells, including at least a biceps curl and, for more able individuals, shoulder forward raise, lateral raise, or press exercises, and leg strength training exercises using a sit-to-stand weighted vest (All Pro Exercise Products, FL) or a waist belt (Rehabus, Lerum, Sweden), or both. The starting weight for sit-to-stand varied between 0 and 12 kg

Participants

People with dementia were eligible if they had a clinically confirmed diagnosis of dementia in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)7 and a standardised mini mental state examination score (sMMSE)8 of greater than 10, were able to sit on a chair and walk 10 feet (3.05 m) without assistance, and lived in the community either alone or with others. We excluded people with acute, unstable physical or terminal illness that would make participation in the exercise programme unsafe.

Study treatments

The interventions and rationale are described in detail elsewhere.7 Physiotherapists and exercise assistants prescribed and delivered interventions in the exercise arm. People with dementia attended an individual assessment where the prescription of aerobic and strength exercises was tailored to their fitness and health status. The assessment included a review of health conditions that required modifications of the exercise prescription (eg, diabetes, cardiovascular conditions, musculoskeletal conditions), and drugs that might be needed during sessions (eg. glyceryl trinitrate sprays, inhalers). Thereafter, people with dementia attended group sessions in a gym twice a week for four months; each session lasted 60 to 90 minutes. We also asked the participants to do home exercises for one additional hour each week during this period. The supervised programme lasted four months, after which we prescribed a more frequent home based programme with a target of unsupervised physical activity or exercise of 150 minutes each week (total). We used behavioural strategies (described elsewhere)9 to promote adherence throughout, and up to three telephone motivational interviews were administered after the supervised programme. The behavioural strategies included guiding participants to choose home exercises or activities that matched their preferences for venue, personal situation, and ease of completion.

Carers provided separate written informed consent for the carer element of the study.

Participants

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of clinical need. Doctors determined additional treatment on the basis of observing home interviews. The training team experienced with the ADAS-cog version of the EQ-5D quality of life measure (scored 0-10, memory scored 0-35, language scored 0-25, higher scores indicate worse impairment) and the ADAS-cog 11 item scale, scored 0 to 70; higher scores indicate worse cognitive impairment) at 12 months. Secondary outcomes at six and 12 months after randomisation were measured using the Bristol activity of daily living index (scored 0 to 60, higher scores indicate worse impairment, carer rated), neuropsychiatric index (scored 0 to 144, higher scores indicate worse behavioural symptoms, carer rated), the three level version of the EQ-5D quality of life measure (scored 0 to 1, higher scores indicate better quality of life), the quality of life Alzheimer’s disease scale (scored 13 to 52, higher scores indicate better quality of life), ADAS-cog subscale at six months, and ADAS praxis, memory, and language subscales at six and 12 months (praxis scored 0-10, memory scored 0-35, language scored 0-25, higher scores indicate worse impairment).}

Carers provided a retrospective assessment of the participant’s falls and fractures for each six month follow-up period. We recorded deaths and data on use of healthcare and social care resources (including the number of physiotherapy sessions, exercise classes, or other structured physical activity programmes outside of the trial) using the client services receipt inventory (participant and carer rated). Follow-up interviews took one and a half hours.

For each participant in the intervention arm we recorded the number of trial exercise sessions attended, the number of minutes spent cycling at low (warm-up), moderate, and high intensity, and the weight lifted and number of repetitions of each strength exercise. Participants repeated the six minute walk test six weeks after starting the classes and we calculated change in walking distance. We recorded the number of telephone contacts made after the end of the sessions and the adherence with physical activity recommendations reported during the course of the call.

At each session, physiotherapists asked participants and their carers if the person with dementia had experienced any adverse events since the last session. They also observed events during sessions, and during phone contacts asked about adverse events. Short episodes of muscular or postural soreness were expected. We defined serious adverse events as those that resulted in death, persistent or important disability or incapacity, were immediately life threatening, or required hospital admission or medical intervention to prevent one of the serious adverse events. We considered any event occurring during supervised or non-supervised exercise sessions and up to two hours after as being related to intervention.

Outcomes for people with dementia

Unless indicated the respondent is the person with dementia. The primary outcome was the Alzheimer disease assessment scale cognitive subscale (ADAS-cog 11 item scale, scored 0 to 70; higher scores indicate worse cognitive impairment) at 12 months. Secondary outcomes at six and 12 months after randomisation were measured using the Bristol activity of daily living index (scored 0 to 60, higher scores indicate worse impairment, carer rated), neuropsychiatric index (scored 0 to 144, higher scores indicate worse behavioural symptoms, carer rated), the three level version of the EQ-5D quality of life measure (scored 0 to 1, higher scores indicate better quality of life), the quality of life Alzheimer’s disease scale (scored 13 to 52, higher scores indicate better quality of life), ADAS-cog subscale at six months, and ADAS praxis, memory, and language subscales at six and 12 months (praxis scored 0-10, memory scored 0-35, language scored 0-25, higher scores indicate worse impairment).
Masking participants, carers, or the teams providing intervention was not possible. Researchers unaware of treatment assignment undertook all baseline and follow-up interviews in the participants’ home. Before each interview, we asked participants and carers not to reveal the treatment they had received. If the allocation was revealed, we assigned a different interviewer to complete the next follow-up. Researchers who undertook data entry and cleaning were unaware of treatment allocation.

Sample size
For the sample size calculation, we considered a between group difference of 2.45 ADAS-cog points in favour of exercise and a baseline standard deviation of 7.8 as the between group difference to be consistent with the conservative effects achieved by commonly used symptomatic drugs (giving a base target of 322).20 We inflated for unbalanced randomisation (n=38) and potential group (cluster) effects within the intervention arm (n=14, inflation factor 1.04), giving a target of 375 (α 0.05, power 80%). We assumed a 20% loss to follow-up (including 10% death), giving a minimum target of 468 (312 intervention: 156 control). P values are two sided. Because of the need to fill exercise cohorts we anticipated that the final sample would be greater than 468.

Statistical analyses
We conducted analyses using intention to treat principles and analysed all people according to their random allocation. A few people with dementia withdrew themselves from the trial or were lost to follow-up. No people with dementia were withdrawn from the trial by investigators. We generated descriptive statistics for the randomised sample and the sample providing data for the primary analysis. Our prespecified strategy was to avoid imputation of missing cases if there were no discernible patterns in the missing data and the randomised and analysed samples were similar. During peer review a statistical reviewer asked for imputation of missing cases, and this is reported.

We used multilevel regression models with random effect for region to estimate treatment effects at each time point, negative binomial regression models for falls, and median regression for non-normally distributed data. We estimated clustering effects associated with exercise group membership. As cluster effects were negligible, we adjusted all estimates for baseline covariates (age, sex, cognitive impairment (sMMSE), region, and the variable being tested) only. Prespecified treatment subgroup analyses included pre-randomisation cognitive impairment (sMMSE ≥20 and <20), type of dementia (ICD clinical coding Alzheimer’s disease versus other), physical performance (EQ-5D mobility no problems versus some problems or confined to bed), and gender (male versus female). We analysed subgroups using statistical tests of interaction, including adjustment for baseline covariates.21 Compliance was defined a priori as attending 75% or more of group sessions (22 out of a maximum 30), consistent with most exercise guidelines.9 To estimate the effect of compliance on the primary outcome we used complier average causal effect (CACE) analysis.22 We calculated dose of aerobic and strength training for compliers, non-compliers, and overall. To test for differences in the baseline characteristics of compliers and non-compliers we used independent sample t tests or non-parametric equivalent.

We summarised the dose of aerobic training as the mean and standard deviation (or median and interquartile range for non-normal data) of the time spent in moderate and high intensity training. Also, as a proportion of the target time set by the physiotherapist before each session. For strength training the dose indicator was the difference between the average of the weight lifted for each exercise over the first four sessions (as it could take a few sessions to establish good form for maximum repetition) and the weight lifted during the final session. As we allowed for a decrease in repetitions to accommodate a greater strength load, we multiplied the amount of weight lifted by the number of repetitions to gain the overall weight lifted.

When available, we used the published recommendations for dealing with missing items within scales. We anticipated non-ignorable item missing data for the ADAS-cog23 and used recognised item level multiple imputation techniques, including baseline cognitive impairment, for the primary analysis.24 We undertook sensitivity analyses for missing ADAS-cog items, including worst score assignment and complete cases.26 In sensitivity analysis we used item response theory analysis23 but could not achieve an adequate fit to the data and therefore is not reported. We ran additional sensitivity analyses to inform whether unmasking of treatment assignment influenced the treatment estimate.

Study monitoring
A trial steering and data monitoring committee reviewed safety, quality, and masked data at six monthly intervals, and approved changes to the statistical analysis plan and protocol. No interim analyses were done, but the trial steering committee/data monitoring committee could halt the trial for safety or ethical concerns. At the point of trial registration, the primary outcome was the mini mental state examination score. Before starting the trial we changed the primary outcome tool to the ADAS-cog. The reason was superior sensitivity to change that enabled a reduction in the sample size and greater comparability with other trials. We obtained appropriate permissions and paid any required fees for use of copyright protected materials.

Patient involvement
The NIHR involved people with dementia and their representatives in specifying the question, including methods, selecting important outcome domains,
and type of intervention through the commissioning process. The study team involved people with dementia, their representatives, and other stakeholders in the development of the intervention and protocol, including detailed feedback on the intervention, questionnaires, approach and invitation, acceptability of procedures, and logistics. Carers of people with dementia were formal members of the study trial steering committee/data monitoring committee. At the end of the study, people with dementia and carers were invited to a joint feedback day with research and clinical staff, and they contributed actively to discussions about the results and interpretation.

Results

Trial progression and recruitment

Between 1 February 2013 and 24 June 2015, 2929 people were screened, 1847 were found potentially eligible and approached, and 494 were randomised: 329 to an exercise programme and 165 to usual care (fig 1). A mean of 2 (SD 1.4) items from the Alzheimer’s disease assessment scale-cognitive subscale (ADAS-cog) were imputed for 18/137 (13%) of participants in the usual care arm and 33/281 (12%) in the exercise arm. Overall, deaths occurred in 5/165 (3%) participants in the usual care arm and 13/329 (4%) in the exercise arm. We carried out the exercise assessment at a median of 15 (interquartile range 9–25) days after randomisation, and the first session commenced at a median of 22 (14–33) days. The median time between attendance at the last exercise session and the first follow-up was 64 (50–80) days. Final follow-up was a median of 371 (365–379) days from randomisation, with no difference between groups.

Sample

Overall, primary outcome data were available for 137/165 (83%) participants in the usual care arm and 281/329 (85%) in the exercise arm. Baseline characteristics for the randomised and analysed samples were well matched (table 1). Recruited men and women did not differ in age (mean difference –0.3 years, 95% confidence interval –1.69 to 1.16) or baseline ADAS-cog scores (–0.2, 95% confidence interval –1.86 to 1.41). More women than men lived alone (73/193 (38%) vs 24/301 (8%), respectively). Most of the people with dementia were able to provide informed consent (376/484, 76%), some required a personal consultee (117/494, 24%), and one required a nominated consultee (1/494, 0.2%).

Intervention

Table 2 shows data on the profile of participants in the exercise arm, attendance, dose of exercise delivered, and physical fitness outcomes by compliance status. Overall, 21 physiotherapists and 17 assistants delivered 1697 face to face training sessions. Most of the participants assigned to the exercise arm (317/329, 96%) attended the physiotherapy assessment, and the proportion assessed as having comorbidity was high (278/317, 88%). The median group size was 6 (interquartile range 5–7). More than 65% (214/329) of the participants were classed as compliers. Men were more likely to comply than women, otherwise there were no differences. Weight lifted improved in all strengthening exercises across the sessions, as did the duration of higher intensity aerobic activity. Over six weeks, the distance walked in six minutes improved by 18.1 m (95% confidence interval 11.6 m to 24.6 m; P<0.001). Most of the participants (245/329, 75%) received three motivational telephone calls after the sessions finished and 217/245 (88%) reported continuing with exercise at home.

Usual care and other interventions

No important differences were found in health and social care resource use (see appendix 1). Less than 1% (3/415) of the participants used structured exercise outside of the trial prescription, less than 4% (15/415) reported attending a physiotherapist’s clinic, and nobody randomised to usual care accessed trial exercise sessions.

Fig 1 | Flowchart of participants through trial. Participants could be ineligible for more than one reason

| Screened (n=2929) |
|-------------------|
| Ineligible (n=1082*): |
| Did not have probable dementia according to DSM IV criteria (n=25) |
| Did not have dementia of mild to moderate severity (MMSE<10) (n=244) |
| Were not able to sit on a chair and walk 10 feet without human assistance (n=239) |
| Were medically unstable to exercise (n=303) |
| Did not live in community (not residential or nursing home) (n=422) |
| Declined (n=1353): |
| Not interested (n=145) |
| No reply (n=65) |
| Other health issues (n=64) |
| Participant commitment (n=40) |
| Carer commitment (n=18) |
| Transport (n=6) |
| Other reason (n=120) |
| Not specified (n=897) |

| Randomised (n=494) |
|-------------------|
| Allocated to usual care (n=165): |
| Withdrew from intervention but remained in follow-up (n=0) |
| Follow-up at 6 months (n=145): |
| Withdrew from trial (n=17) |
| Died (n=1) |
| Lost to follow-up (n=2) |
| Follow-up at 12 months (n=137): |
| Withdrew from trial (n=21) |
| Died (n=5) |
| Lost to follow-up (n=2) |
| Analysed at 12 months (n=137): |
| Excluded from analysis (n=28): |
| Withdrew from trial (n=21) |
| Died (n=5) |
| Lost to follow-up (n=2) |
| Allocated to exercise programme (n=329): |
| Withdrew from intervention but remained in follow-up (n=33) |
| Follow-up at 6 months (n=300): |
| Withdrew from trial (n=18) |
| Died (n=5) |
| Lost to follow-up (n=6) |
| Follow-up at 12 months (n=281): |
| Withdrew from trial (n=24) |
| Died (n=13) |
| Lost to follow-up (n=11) |
| Analysed at 12 months (n=281): |
| Excluded from analysis (n=48): |
| Withdrew from trial (n=24) |
| Died (n=13) |
| Lost to follow-up (n=11) |

* Participants have one or more reasons for ineligibility
Adverse events
Twenty five adverse events occurred (eight were possibly related, nine probably related, and eight definitely related) and four serious related adverse events (one hospital admission for exercise induced angina, two injurious falls, and one case of substantially worsening hip pain) in the exercise arm and no reports in the usual care arm. In the exercise arm an adverse event was reported by 23/329 (7.0%, 95% confidence interval 4.7% to 10.3%) participants.

Outcomes
Table 3 and figure 2 show the treatment effect estimates. Cognitive impairment declined over the 12 month follow-up in both trial arms. The exercise arm had higher global ADAS-cog scores at 12 months (adjusted mean difference −1.4, 95% confidence interval −2.6 to −0.2). Higher scores indicate worse cognition, although the average difference was less than the prespecified between group difference, and clinical relevance was uncertain. Sensitivity analyses for the primary outcome were consistent in the direction of effect regardless of the method of accounting for missing data at item level (table 3). Imputation for missing cases yielded a complete intention to treat estimate of adjusted mean difference −1.3 (95% confidence interval −2.4 to −0.2). No evidence was found of differences in other secondary outcomes, including the rate of falls over 12 months (incident rate ratio 1.1, 95% confidence interval 0.8 to 1.6; P=0.69).

The complier average causal effect estimate for the primary outcome was −2.0 (95% confidence interval −3.87 to −0.22) indicating worse cognitive impairment (below the prespecified between group difference) in those with higher attendance of sessions. No differences were found in carer burden or quality of life between the two interventions. There were no statistically significant subgroup effects (table 4).

At 12 months, interviewers reported that they knew the treatment assignment in 11/132 cases (8%) in
### Table 2 | Intervention data by compliance status. Values are numbers (percentages) unless stated otherwise

| Participants | Compliers (n=214) | Non-compliers (n=115) | All (n=329) |
|--------------|-------------------|-----------------------|-------------|
| **Demographics** | | | |
| Mean (SD) age (years) | 76.5 (7.8) | 77.7 (8.1) | 76.9 (7.9) |
| Men | 144 (67) | 51 (44) | 195 (59) |
| Mean (SD) ADAS-cog score (imputed) | 21.9 (9.7) | 20.5 (9.4) | 21.4 (9.6) |

| **Medical conditions** | | | |
| Heart or circulatory | 102 (48) | 52 (50) | 154 (49) |
| Glycemic tinnitus rate | 18 (8) | 13 (13) | 31 (10) |
| Lung disease | 22 (10) | 18 (17) | 40 (13) |
| Inhaled | 22 (10) | 14 (14) | 36 (11) |
| Diabetes | 38 (18) | 21 (20) | 59 (19) |
| Neurological condition | 42 (20) | 15 (15) | 57 (18) |
| Limiting joint or muscle pain | 117 (55) | 60 (58) | 177 (56) |
| Broken bones in past 6 months | 14 (6.5) | 8 (8) | 22 (7) |
| Mental illness | 65 (30) | 45 (44) | 110 (35) |

### Table 3 | Main estimates of treatment effect

| Outcomes | 6 months | | | | 12 months | | | |
|----------|----------|----------|--------------|----------|----------|----------|--------------|----------|
| | Usual care | Exercise programme | | Adjusted estimate (95% CI); P value | Usual care | Exercise programme | | Adjusted estimate (95% CI); P value |
| | No Mean (SD) | No Mean (SD) | | | No Mean (SD) | No Mean (SD) | | |
| ADAS-cog: cognitive subscale | 145 22.4 (9.4) | 298 22.9 (11.6) | | -0.6 (-1.6 to 0.4); 0.24 | 137 23.8 (10.4) | 278 25.2 (12.3) | | -1.4 (-2.6 to -0.2); 0.03 |
| Sensitivity analyses: | | | | | | | | |
| Complete case analysis | 135 21.4 (8.5) | 280 21.7 (10.3) | | -0.7 (-1.7 to 0.4); 0.20 | 119 22.4 (9.7) | 245 22.9 (10.6) | | -1.7 (-3.0 to -0.4); 0.01 |
| Worst score analysis | 145 23.8 (12.8) | 293 23.1 (12.5) | | -0.4 (-0.8 to 0.17); 0.52 | 137 25.5 (13.7) | 278 26.6 (14.8) | | -0.9 (-2.6 to 0.7); 0.27 |
| ADAS-cog subscales: | | | | | | | | |
| Language* | 145 2 (1 to 5) | 299 2 (0 to 5) | | 0.001 (-0.4 to 0.56); 1.00 | 137 2 (0.7 to 5) | 280 2 (1 to 7) | | -0.2 (-0.8 to 0.45); 0.61 |
| Memory | 145 17.3 (5.6) | 298 17.3 (6.9) | | 0.5 (-1.2 to 0.3); 0.22 | 137 18.1 (5.6) | 279 18.5 (6.7) | | 0.8 (-1.6 to 0.2); 0.06 |
| Praxis* | 145 2 (1 to 3) | 299 1 (1 to 3) | | -0.001 (-0.2 to 0.2); 1.00 | 137 1 (1 to 3) | 281 2 (1 to 3.9) | | 0.1 (-0.4 to 0.2); 0.38 |
| EQ-SD | | | | | | | | |
| Score (self report) | 139 0.83 (0.21) | 292 0.80 (0.21) | | 0.02 (-0.01 to 0.06); 0.24 | 131 0.82 (0.25) | 261 0.81 (0.22) | | -0.002 (-0.04 to 0.004); 0.93 |
| VAS score (self report) | 138 78.7 (18.8) | 292 75.4 (20.6) | | 0.1 (-3.4 to 3.6); 0.94 | 124 78.3 (19.4) | 261 75.5 (19.3) | | 1.4 (-3.4 to 5.2); 0.46 |
| Score (proxy report) | 134 0.65 (0.29) | 277 0.64 (0.27) | | -0.01 (-0.06 to 0.03); 0.53 | 128 0.60 (0.32) | 259 0.60 (0.28) | | -0.02 (-0.07 to 0.03); 0.43 |
| EQ-SD VAS (proxy report) | 135 65.4 (20.5) | 278 66.1 (20.1) | | -0.6 (-4.3 to 3.1); 0.74 | 128 65.6 (19.9) | 260 65.0 (20.0) | | 1.2 (-4.4 to 6.8); 0.52 |
| EQ-SD 5Q (score report) | 132 0.77 (0.24) | 277 0.76 (0.23) | | -0.004 (-0.06 to 0.03); 0.84 | 129 0.78 (0.23) | 261 0.76 (0.24) | | -0.02 (-0.04 to 0.00); 0.94 |
| EQ-SD 5Q (Vas report) | 136 72.4 (20.7) | 277 73.4 (19.7) | | -0.1 (-4.7 to 1.8); 0.38 | 129 75.1 (18.7) | 261 75.4 (18.6) | | 0.2 (-2.9 to 3.3); 0.90 |
| ZBI (carer report) | 122 32.9 (17.1) | 273 31.9 (16.0) | | 0.0 (-2.0 to 2.1); 0.96 | 125 32.7 (16.6) | 256 34.5 (16.1) | | -0.5 (-2.8 to 1.7); 0.64 |

### Notes

- **ADAS-cog**: Alzheimer’s disease assessment scale-cognitive subscale.
- **EQ-SD**: European quality of life measure; VAS=visual analogue scale; ZBI=Zarit burden interview; QoL-AD=quality of life Alzheimer’s disease scale; NPI=neuropsychiatric index; BADL=Bristol activity of daily living index.
- Estimates are random models adjusted for age, sex, site, baseline mini mental state examination score and baseline value of the outcome variable being estimated.
- *Data are not normally distributed estimates and are obtained from median regression. Descriptive statistics are median and interquartile range.
- **ADAS-cog**: ADAS-cog Alzheimer’s disease assessment scale—cognitive subscale.
- **EQ-SD**: EQ-SD = European quality of life measure; VAS = visual analogue scale; ZBI = Zarit burden interview; QoL-AD = quality of life Alzheimer’s disease scale; NPI = neuropsychiatric index; BADL = Bristol activity of daily living index.
- Estimates are random models adjusted for age, sex, site, baseline mini mental state examination score and baseline value of the outcome variable being estimated.
- *Data are not normally distributed estimates and are obtained from median regression. Descriptive statistics are median and interquartile range.

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the usual care arm and 94/276 (33%) in the exercise arm (overall 26%). In the usual care arm 10 of the 11 (90%) assignments were identified correctly and in the exercise arm this was 90 out of 94 (96%) assignments. Including masking status in the covariate adjustment did not alter the treatment effect estimate.

**Discussion**

A four month aerobic and strengthening exercise programme of moderate to high intensity added to usual care does not slow cognitive decline in people with mild to moderate dementia. The exercise improved physical fitness in the short term, but this did not translate into improvements in activities of daily living, behavioural outcomes, or health related quality of life. There is the possibility that the intervention could worsen cognition.

**Comparison with previous studies**

The results disagree with several small studies. Most previous studies are single centre and many have uncertain allocation concealment and poor masking of outcome assessment. Smaller studies are more likely to draw erroneous conclusions. Previous studies might not have achieved as high a dose of exercise and some have mixed exercise and cognitive training making it difficult to isolate the effectiveness of different elements of the training programme. For example, the Finnish Alzheimer disease exercise (FINALEX) study compared a 12 month combined exercise, strength and balance exercise programme at either home or in a group supervised setting versus usual care in people with mild to moderate dementia. Combined home exercise and cognitive training had a benefit on functional independence, a marginal benefit on executive function and falls, but no benefits on global cognitive function or mobility. Several other relatively large studies reported null effects on global cognition.

**Strengths and limitations of this study**

In comparison with previous trials, we recruited a substantially larger sample size, used a measure of cognitive impairment recommended as a core outcome in consensus guidelines, and maintained high levels of follow-up. We used robust allocation concealment and masked outcome assessment. Loss to follow-up was low and baseline characteristics for the randomised and analysed samples were similar. We conducted a range of sensitivity analyses. Analysis of both observed and fully imputed data on cognitive impairment yielded a similar treatment effect estimate. No suggestion of a hidden effect in subgroups of mobility, cognition, sex, and underlying cause of dementia was found. As expected, the 95% confidence intervals within each subgroup were broader but consistent with the overall finding. We delivered a relatively high dose of exercise, with good compliance. The dose of strengthening exercise was at least equal to previous work in older people without dementia, and much higher than that achieved in residential care settings where people are more frail and a similar intervention was found to improve balance but not cognitive or activities of daily living status. Participants and carers were not masked to allocation, but this is an unavoidable limitation. We

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**Table 4 | Subgroup analyses of 12 month ADAS-cog (imputed) outcome. Values are number of participants, mean (standard deviation) unless stated otherwise**

| Subgroups | Usual care | Exercise programme | Within stratum: effect estimate (95% CI) | Interaction effect (95% CI) | P value for interaction |
|-----------|------------|-------------------|----------------------------------------|---------------------------|------------------------|
| Sex:      |            |                   |                                        |                           |                        |
| Male      | Baseline   | 85; 21.7 (8.4)    | 86; 23.9 (11.4)                        | -1.2 (-2.78 to 0.46)      | -0.6 (-3.17 to 1.88)  | 0.62                   |
|           | 12 months  | 168; 20.6 (8.7)   | 166; 23.9 (11.8)                       |                           |                        |                        |
| Female    | Baseline   | 50; 20.7 (6.8)    | 51; 23.7 (8.5)                         | -1.8 (-3.60 to 0.08)      |                        |                        |
|           | 12 months  | 113; 22.2 (10.6)  | 112; 27.3 (12.9)                       |                           |                        |                        |
| sMMSE score: |            |                   |                                        |                           |                        |                        |
| <20       | Baseline   | 36; 30.5 (7.6)    | 36; 34.3 (10.9)                        | -2.8 (-5.32 to -0.27)     | 1.8 (-0.98 to 4.50)   | 0.21                   |
|           | 12 months  | 85; 31.1 (8.3)    | 84; 37.7 (10.8)                        |                           |                        |                        |
| ≥20       | Baseline   | 99; 18.0 (4.6)    | 101; 20.1 (7.2)                        | -0.9 (-2.32 to 0.46)      |                        |                        |
|           | 12 months  | 196; 17.0 (6.1)   | 194; 19.8 (8.4)                        |                           |                        |                        |
| EQ-3D-3L mobility score: |            |                   |                                        |                           |                        |                        |
| No problems walking | Baseline | 102; 21.9 (8.1)  | 103; 24.5 (10.5)                       | -1.3 (-2.65 to 0.10)      | 0.00005 (-2.86 to 2.86) | 1.00                   |
|           | 12 months  | 207; 22.5 (9.6)   | 204; 26.6 (12.8)                       |                           |                        |                        |
| Some problems/confined to bed | Baseline | 32; 19.5 (6.5)   | 33; 21.7 (10.0)                        | -1.6 (-4.21 to 1.00)      |                        |                        |
|           | 12 months  | 74; 18.0 (8.1)    | 74; 21.4 (10.0)                        |                           |                        |                        |
| Type of dementia: |            |                   |                                        |                           |                        |                        |
| Alzheimer's disease | Baseline | 107; 20.9 (7.9)  | 108; 23.7 (10.0)                       | -1.1 (-2.41 to 0.29)      | 1.3 (-1.81 to 4.35)   | 0.42                   |
|           | 12 months  | 229; 21.5 (9.5)   | 227; 25.6 (12.4)                       |                           |                        |                        |
| Other (mixed, vascular, other types) | Baseline | 28; 23.2 (7.5)   | 29; 24.5 (11.8)                        | -2.7 (-5.58 to 0.16)      |                        |                        |
|           | 12 months  | 52; 20.1 (8.9)    | 51; 23.5 (11.9)                        |                           |                        |                        |

sMMSE=standardised mini mental state examination, EQ-3D-3L=three level European quality of life measure.

*Adjusted estimates from multilevel regression models with random effect for region and adjustment for age, sex, sMMSE score, and baseline value of dependent variable.
were successful in masking three quarters of interviews for the primary time point. The level of unmasking was higher in the exercise arm but it seems unlikely that this would account for our findings. Physical fitness improved, but we are limited to data in the exercise arm and during the structured exercise intervention period only. Hence we cannot conclude definitively that the intervention improves physical fitness. It is unlikely that fitness would have improved in the usual care arm as there was no evidence of engagement in exercise or physiotherapy. Subgroup analyses might be underpowered as the proportions in the various strata were not balanced. We asked carers to recall falls events instead of using monthly calendar diaries. This might result in underestimation of the overall number of falls but is unlikely to affect the between group difference. We collected data on adverse events related to exercise in the intervention arm only. The period of structured exercise in our study might have been too short to produce positive benefits. We believe this unlikely as changes in physical fitness had occurred during the intervention but did not transfer into other clinically meaningful benefits. Withdrawal of the structured exercise programme by six months might have led to an accelerated decline in cognitive impairment mediated through social and affective mechanisms.

The numbers of people who declined participation in the trial was high and suggests that exercise might not be an attractive proposition. We recruited more men than women even though dementia is more common in women in western Europe. Compliance was better in men. Women might have found the offer or experience of exercise unattractive. Alternatively, more women were living alone, with the associated difficulties of motivating and getting themselves to sessions. We did not include an attention control, as our intention was for a pragmatic trial.

**Interpretation**

The study was designed as a superiority trial. Slowing cognitive decline was an ambitious target, but we anticipated at least a benefit in functioning in activities of daily living given broader knowledge about the effects of improved physical fitness. It is possible that cognition might have been worsened by the intervention. Whether the effect on cognitive impairment we observed is important is uncertain. We did not prespecify a value for a negative effect, but the average effect observed was smaller than our prespecified superiority target of 2.45 ADAS-cog points. An influential international consensus group suggests that a between group difference of 2 points (or 25%) might be worthwhile depending on the cost and safety profile of the intervention. Treatments in common use are associated with differences smaller than 2 points. In the context of the overall average annual decline in cognitive impairment, the decline in the usual care arm was consistent with published expectations, and the treatment difference was at least half as much as the annual rate of decline. Survival is on average 4.5 years in mild to moderate dementia. Worsening in cognitive impairment was greater in those who complied with the intervention and is physiologically feasible. High intensity training in healthy humans can have negative short term effects, including slow reoxygenation of cortical areas with a transient reduction in executive function. Inflammation induced by higher levels of exercise might also be implicated.

**Recommendations and policy implications**

Moderate to high intensity aerobic and strength exercise cannot be recommended as a treatment option for cognitive impairment in dementia. Future trials should explore other forms of exercise, including psychomotor protocols that are commonly used in long term neurological conditions where the primary intent is improving physical functioning. Investigators should consider the possibility that some types of exercise intervention might worsen cognitive impairment and of a “rebound” effect if the exposure to an intervention is to be time limited.

This exercise programme is not an effective way to manage cognitive impairment, functional impairment, or behavioural disturbances in older people with mild to moderate dementia.

**Conclusion**

A four month period of moderate to high intensity aerobic and strength exercise training, and ongoing support to exercise does not slow cognitive decline and might worsen cognitive impairment in people with mild to moderate dementia. Although moderate to high intensity exercise improves physical fitness, no clinical outcomes that we studied responded in a positive direction.

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**Contributors:** SEL (chief investigator): conceived and designed the study and had overall responsibility for the study design and delivery. She is the guarantor. DM did the statistical analysis. NA developed and implemented the intervention and was training and quality assurance lead for the intervention. SD was responsible for the trial logistics and management, and writing and reviewing of...
the manuscript. IK was responsible for the economic analysis of the trial. RL is a grant holder and was responsible for the statistical analysis. HC was responsible for recruitment and guidance on strategies for recruitment and testing procedures. AMS is a grant holder and lead ethicist and provided the framework for consent and advice and guidance on ethical issues during the trial. VN was responsible for trial management and was the recruitment lead and was responsible for training and quality assurance. SP is a grant holder and was responsible for the economic analysis and writing and reviewing of the manuscript. BS was responsible for study design and conduct, clinical responsibility, and writing and reviewing of the manuscript. All authors have contributed to drafting the manuscript and approving the final version.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved by national ethics review committees (REC No 11/SW/0232) and research governance departments in each organisation.

Data sharing: The relevant anonymised patient level data, full dataset, technical appendix, and statistical code are available on reasonable request from the corresponding author. Consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low.

Transparency: The lead author (SEL) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary information: appendix 1