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Physical Activity for Older Adults with Alzheimer's Disease: a Randomized Trial

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Abstract

Many observational research has proven that physical activity reduces the chance of cognitive decline; however, proof from randomized trials is lacking. To determine whether or not physical activity reduces the rate of cognitive decline amongst older adults at hazard. Randomized controlled trial of a 24-week physical activity intervention performed among 2016 and 2018 in Riyadh, Saudi Arabia. Assessors of cognitive characteristic were blinded to group membership. We recruited volunteers who reported memory issues but did now not meet standards for dementia. two hundred fifty individuals elderly 50 years or older had been screened for eligibility, seventy-six have been not eligible, and sixty-four refused to take part. a complete of one hundred ten contributors were randomized for the evaluation. participants had been randomly allocated to an education and typical care group or to a 24-week home-based program of physical activity. on this examine of adults with subjective memory impairment, a 6-month application of bodily hobby provided a modest improvement in cognition over an 18- month follow-up duration.

1. INTRODUCTION

The variety of older adults dwelling with Alzheimer disease (AD) is predicted to growth from the present day 26.6 million to 106.2 million by 2050 see [1]. If illness on set may be delayed via 12 months, 9.2 million fewer cases of AD might occur global. For this reason, tries had been made to perceive people who are at accelerated hazard of AD and to check interventions that might postpone the development of prodromal signs and symptoms to complete-blown dementia. The outcomes from observational research advice that older folks that are free of dementia however record memory decline or show goal evidence of cognitive impairment are more likely to broaden ad through the years [2, 3].

Seven clinical trials have investigated whether or not cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), vitamin E, piracetam, and rofecoxib (a cyclooxygenase 2 inhibitor) can prevent cognitive decline and development to dementiain older adults with mild cognitive impairment. In an ordeal with the aid of Petersen et al [4] 769 participants with mild impairment to dementia over four years stated in addition negative findings [5]. Preliminary results from two galantamine trials that have not begun to be finished had been also negative, as have been the findings from the piracetam and rofecoxib trials [6, 7]. Different strategies to prevent cognitive decline and dementia in human beings at danger are presently being examined, however available effects had been combined for B vitamins, statins, and antihypertensive therapy [8- 12].

Several observational studies have observed that individuals who are physically lively appear less in all likelihood than sedentary persons to experience cognitive decline and dementia in later life. Weuve et al [13] said that better tiers of bodily activity over 2 years the various 18766 women within the Nurses' health study have been related to progressed cognitive scores. Further, Abbott et al [14] stated that guys who walk at least 2 miles a day are 1.8 instances much less possibly than sedentary men to broaden dementia over a follow-up length of 6 years.

Next potential research confirmed that physical activity is associated with decreased incidence of dementia and showed that the affiliation of bodily activity and cognitive characteristic is apparent even if exercise is restricted to later life [15-17]. However, confirmatory evidence from randomized trials remains lacking. We designed the existing randomized trial to test whether or not a 24-week home-based bodily activity intervention reduces the rate of cognitive decline amongst older adults at increased risk of dementia.

2. METHODOLOGIES PARTICIPANTS

110 community-dwelling older adults diagnosed with AD recruited across three sites in Saudi Arabia (Riyadh, Dammam, and Jeddah). Participants will be included in the study if they satisfy the following criteria: (i) diagnosed with probable or possible AD according to NINCDS-ADRDA criteria, (ii) score of 10 or greater on the Standardized Mini Mental State Examination (SMMSE), (iii) community dwelling, (iv) no clinically significant depression, (v) understands written and spoken Arabic, (vi) contact with a friend or family member (carer) for at least 10 hours per week, who is also willing to participate in the trial, and (vii) no other major neurological history or medical condition that contraindicates PA.

Participants will be excluded if they unable to walk alone or require a walking aid for balance, show evidence of clinically enormous aphasia or pervasive depression, have a risky or life-threatening medical situation, or are collaborating in any other RCT.

Analysis of ad might be showed through clinical statistics received from the participant's treating general practitioner and specialist. Those statistics can be reviewed with the aid of participants of the studies group who are either experienced

Geriatricians or old Age Psychiatrists to verify the participant's suitability for inclusion.

3. ASSESSMENT OF PHYSICAL ACTIVITY

Community Healthy Activities Program for Seniors (CHAMPS) survey was used to assess physical activity. Participants were asked to complete the CHAMPS questionnaire two times during the 2-week screening or baseline period to familiarize them with all questions. Data from the first questionnaire were disregarded, whereas the second provided the data for the following summary measures.

Physical activity measures included minutes per weeks penton all exercise-related activities, minutes per week spent on all moderate-plus activities, and calories expended in all moderate-plus activities.

Moderate-plus activities included moderate, hard, and very hard intensity activities (eg, brisk walking, ballroom dancing, gym circuit, or swimming).In addition, all participants wore a pedometer (Digi-walkers-700, YamaxInc, Tokyo, Japan) during the 7-day baseline assessment with the CHAMPS, as well as during the week preceding the 6-, 12-, and 18-month assessments. This provided an objective and valid measure of activity summarized as the total number of steps walked in a day. Participants recorded this information in a diary, in which information about when the pedometer was on or off was also registered. When participants performed nonstop physical activity (such as swimming or cycling), the intensity of the activity was determined and the equivalent number of steps estimated and added to the daily record, as outlined by Miller et al. Because 10000 steps per day are associated with improved health outcomes, participants with a weekly step count greater than or equal to 70000 were classified as active and the remainder, non-active.

4. ASSESSMENT OF COGNITIVE FUNCTION, DEPRESSION, AND QUALITY OF LIFE

The cognitive section of the Alzheimer Disease Assessment Scale (ADAS-Cog) was the primary outcome measure of the study. The scale consists of 11 brief cognitive tests assessing memory, language, and praxis. Scores range from 0 to70, with higher scores indicating greater severity of cognitive impairment. Secondary cognitive measures of interest included (1) the Cognitive Battery of the Consortium to establish a Registry for Alzheimer Disease total number of words recalled with (range, 0-10) and without (range, 0-30) delay, (2) total score on the Digit Symbol Coding Test (possible scores, 0-133), and (3) verbal fluency (number of words beginning with F, A, and S that the individual can say in a minute) as measured by the Delis-Kaplin executive function Battery.

Participants were also rated according to the Clinical Dementia Rating sum of boxes teach assessment. Premorbid IQ was measured with the Cambridge Contextual Reading Test. Throughout the trial, we monitored the frequency and severity of depressive symptoms with the Beck Depression Inventory (range, 0-63, with higher scores indicating greater levels of depressive symptoms), and quality of life with the Medical

Outcomes 36 Item Short-Form (SF-36) Health Survey physical and mental composite scores (both have a population norm of 50 points, with lower scores indicating worse quality of life,).

5. RANDOMIZATION

At the end of the baseline assessment, participants were randomly allocated to the physical activity program or usual care control according to a list of computer-generated random numbers in blocks of 8 (4 persons randomly allocated to each group). Allocation numbers were kept in sealed containers and were drawn by an investigator not directly involved in the recruitment or assessment of participants. Due to the nature of the intervention, participants were not blinded to group membership, but research personnel undertaking cognitive assessments were. To ensure compliance with these procedures, research staff conducting the physical activity intervention were housed in a different building and received independent supervision. Participants were explicitly asked at the beginning of the trial and at each subsequent assessment not to discuss information regarding the intervention with research staff conducting the rating of cognitive function. Similarly, research staff conducting the cognitive assessment were instructed not to discuss with the participants any aspects of the intervention. The physical activity research staff and the cognitive assessment research staff were supervised by different investigators of the FABS team.

6. CONTROL GROUP

Participants in this group received educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking but not about physical activity. Participants in the physical activity group were also offered these educational materials.

6.1 Physical Activity Intervention

The aim of the intervention was to encourage participants to perform at least 150 minutes of moderate-intensity physical activity per week, 36 which participants were asked to complete in three 50-minute sessions each week. The regimen of 3 sessions week was selected because previous experience had shown that this format was acceptable to participants and because it was logistically and financially more practical for those who choose activities that required classes or a center venue. Those who were already achieving the recommended target at baseline were encouraged to add another 50 minutes per week (1 session) to their individual activity level. The individualized home-based physical activity program and the workbook for the behavioral intervention package were delivered during a 60-minute interview with a trained physical activity staff member. The most frequently recommended type of activity was walking. However, participants could choose other forms of exercise to achieve the three 50-minute sessions per week. Twelve participants chose to include some light strength training exercise in their program.

These were participants who were already active and had had previous experience with circuit gym exercise. Apart from 1 participant, all chose walking or another aerobic exercise as well as the strength training activities. Participants further received mail-out newsletters in weeks 2, 8, 14, 20, 32, 40, 65, and 72 to reinforce the key messages of the program. The intervention did not include home-based equipment.

All participants were asked to use a simplified diary to record their physical activity and to return the diaries to the physical activity supervisor every month by reply paid post. Adherence was calculated from the number of sessions recorded in the monthly diaries and was defined as the percentage of physical activity completed compared with total physical activity prescribed.

6.2 Behavioral Intervention

To enhance adherence to the program, participants also received a modified behavioral intervention package based on social cognitive theory. The package was delivered via a workshop, a manual, newsletters, and telephone calls. The manual and the newsletters contained information on exercise programs, rewards, goal setting, time management, barriers to activity, and safe exercise.

During the 24-week intervention, participants underwent a structured interview by telephone to monitor the progress of the physical activity program and to encourage continuing compliance. (The original protocol specified that 6 telephone calls would take place during the intervention, but due to limited resources and the need to attempt to contact participants several times before being able to reach them, the average the number of calls was reduced to a mean [SD] of 2.0 [1.1] and each call lasted a mean of 10.5 [9.0] minutes.)

6.3 Follow-up Visits

We repeated the assessment of physical activity, cognitive function, mood, and quality of life at 6, 12, and 18 months after baseline. Participants in the physical activity intervention were encouraged to remain physically active, with no further intervention offered except for 4 newsletters, as described above.

6.4 Power Calculation

We collected 12-month prospective ADAS-Cog data on an independent sample of older adults with subjective memory complaints living in Perth. The results showed a mean (SD) increase of 3.5 (4.5) points over that period. Because the participants were more likely to be at risk of impairment than those in the independent sample, we then estimated that the ADAS-Cog scores of participants not receiving the physical activity intervention would deteriorate an additional 2.5 points (total, 6.0 points; SD, 4.5) per year. This is the smallest difference considered clinically meaningful in clinical treatment trials. The participation of 84 volunteers in each of the 2 groups (n=168) at

baseline resulted in power of 90% with set at .05. We estimated a dropout rate of 20%, which led to the recruitment of 170 participants with a power of 80% (85 randomly allocated to each group).

6.5 Analysis of the Data

For normally distributed continuous variables, arithmetic means and SDs were calculated. For logarithmically transformed continuous variables, geometric means and SDs were computed. For baseline comparison between exercise and usual care control groups, the Pearson method was used in the investigation of categorical data, the statistical result being distributed as 2. For normally distributed variables in the analysis of basic characteristics between the 2 groups, *t* tests were conducted.

The 3 follow-up time points were conducted at 6, 12, and 18 months. We used 2 different analytical strategies to determine between-group differences. The primary analysis was based on intention to-treat analysis using the multiple imputation procedure of SAS. For positively skewed variables, log transformations were applied prior to imputations.

Baseline, 6-, 12-, and 18-month scores were included in the imputation model in addition to sex, education, premorbid IQ, and marital status. We conducted 5 imputations using a sequential chain of interactions with a burn of 200 interactions followed by 100 interactions between successive imputations. Each imputed data set was analyzed using a mixed-effect model with repeated measures, and parameter estimates were then averaged across data sets. The intention to-treat analysis was then followed by a complete-case analysis, in which participants with valid data at all-time points were included in the analysis.

Repeated measures procedure was used in an analysis of covariance (ANCOVA) in both the intention to-treat and complete-case analyses. For intention-to-treat data, a mixed model with repeated measures in SAS was used while for complete-case data, a general linear model for repeated measures ANCOVA in SPSS was used. Four time points were treated as a within-participants factor (effect overtime) and the differences between the exercise and usual care control group were treated as a between-participants factor. The interactions between within- and between participants' factors were also examined in the above analyses. Covariates such as age, sex, educational level, marital status, and premorbid IQ were included in the multivariate model. In addition, data from each follow-up time point were subtracted from baseline for each participant to examine the magnitude of change over time. Repeated measures ANCOVA analyses were applied to evaluate change from baseline in the same manner described above.

Finally, post hoc analyses investigated the impact of *APOE* genotype on cognitive function in relation to the intervention, as well as the impact of the intervention for participants with mild cognitive impairment. All statistical significance tests were 2-sided, and =.05 was considered statistically significant.

7. RESULTS

Two hundred fifty individuals were screened for eligibility over the telephone. One hundred ten older adults met criteria and consented to take part in the trial, of whom 38 had amnestic mild cognitive impairment single domain; 17, amnestic mild cognitive impairment multiple domain; and 9, nonamnestic mild cognitive impairment. TABLE 1 shows their demographic and clinical characteristics.

Table 1. Baseline Characteristics of Trial Participants

	Exercise (n = 55)	**Control (n = 55)**
Age, mean (SD), y	65.5 (7.4)	65.1 (7.8)
Women, No. (%)	30 (54.5)	32 (58.1)
Educational level, mean (SD), y	11.3 (2.9)	10.6 (3.4)
Married or de facto, No. (%)	42 (76)	47 (85)
Risk factors, No. (%)		
Ever heavy smoker	15 (27)	14 (25)
Current smoker	2 (4)	3 (5)
Heart disease	7 (13)	9 (16)
Hypertension	19 (35)	18 (34)
Arthritis	14 (25)	16 (29)
Asthma	11 (20)	9 (16)
Health and mental health score, mean (SD)		
BDI	3.1 (2.8)	4.1 (1.9)
PCS	41.4 (8.3)	49.4 (7.7)
MCS	43.1 (5.5)	48.1 (6.1)
All moderate-intensity plus activities, mean (SD), min/wk	164.2 (5.0)	167.8 (4.0)
Total steps/wk, mean (SD)	49735 (22 375)	53927 (24956)
Active participants: reached target steps/wk, No. (%)	16 (29)	14 (25)
Premorbid IQ, mean (SD)	104.1 (4.8)	107.1 (5.2)
Assessment score, mean (SD)		
ADAS-Cog	5.8 (1.8)	6.0 (1.9)
Word list total immediate recall	15.43(3.2)	16.58 (3.7)
Word list delayed recall	5.6 (3.4)	5.2 (3.5)
Digit symbol coding	51 (14)	54 (13)
Verbal fluency total score	41 (11.1)	38 (12.6)
CDR sum of boxes	1.0 (0.7)	1.0 (0.7)
APOE ∑4 carrier, No. (%)	21 (38.8)	23 (41.8)

Clinical subtype, No. (%)		
Subjective memory complaints only	29 (52)	25 (45.4)
Amnestic MCI	31 (56.3)	33 (60)
Nonamnestic MCI	4 (7.2)	3 (5.4)

Abbreviations:
ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale;
BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating; IQ, premorbid IQ as determined by the Cambridge Contextual Reading Test; MCI, mild cognitive impairment; MCS, Medical Outcomes 36-Item Short Form (SF-36) mental component summary; PCS, SF-36 physical component summary.

Effect of the Intervention on Cognitive Function, Mood, and Quality of Life

TABLE 2 shows intention-to-treat changes in cognitive scores, mood, and quality of life over 18 months by group. By study end, participants in the exercise group had better ADAS-Cog scores than those in the usual care control group (*P*= .05).

Table 2. Effects of the Intervention and Time on Cognitive Outcomes, Mood, and Quality of Life of Participants (Intention-to-Treat Method Using Multiply Imputed Data)

	Mean Difference From Baseline (95% CI)		***P* Value ANCOVA for Repeated Measures**	
	Exercise Group (n = 55)	**Control Group (n = 55)**	**Between Participants**	**Within Participants**
Total ADAS-Cog score				
6	-0.18(-0.21 to 1.24)	1.15 (1.02 to 2.32)	.05	.68
12	-0.47 (-2.05 to 0.9)	0.17 (1.36 to 1.14)		
18	-0.65 (-2.17 to 0.73)	0.07 (-1.16 to 1.38)		
Word list total immediate recall				
6	1.124 (1.02 to 2.47)	1.31 (0.81 to 2.01)	.57	.21
12	1.234 (1.3 to 2.7)	1.57 (1.09 to 2.24)		
18	1.594 (1.48 to 2.93)	1.59 (1.1 to 2.28)		
Word list delayed recall				
6	0.54 (0.43 to 1.57)	0.71 (0.59 to 1.17)	.03	.20
12	0.46 (0.33 to 1.52)	-0.09 (-0.06 to 0.62)		
18	0.85 (0.31 to 1.8)	0.46 (0.24 to 0.72)		
Digit symbol coding total				
6	3.52(2.05 to 4.78)	4.23 (2.56 to 5.31)	.25	.27
12	3.65 (2.21 to 4.88)	4.69 (3.05 to 5.74)		
18	4.62 (3.16 to 5.88)	3.82 (2.07 to 4.96)		
Verbal fluency total score				
6	2.28 (1.1 to 4.42)	0.49 (-0.64 to 2.09)	.16	.48
12	3.17 (2.18 to 4.98)	0.94 (-0.49 to 2.42)		

18	2.3 (1.03 to 4.44)	1.48 (-0.26 to 3.69)		
CDR sum of boxes				
6	0.64 (0.58 to 0.71)	0.63 (0.47 to 0.58)	.03	.04
12	0.59 (0.54 to 0.65)	0.58 (0.43 to 0.53)		
18	0.47 (0.44 to 0.5)	0.4 (0.27 to 0.57)		
BDI score				
6	-0.14 (-0.87 to 0.58)	-0.15 (-1.02 to 0.53)	.56	.20
12	0.05 (-0.72 to 0.82)	0.16 (-0.69 to 0.8)		
18	0.34 (-0.57 to 1.25)	0.09 (-0.84 to 0.82)		
PCS score				
6	-3.24 (-4.81 to-1.67)	-3.8 (-5.5 to -2.3)	.88	.41
12	-3.69 (-5.13 to -2.26)	-3.13 (-5.07 to -1.39)		
18	-4.05(-5.88 to -2.22)	-4.09(-5.92 to -2.47)		
MCS score				
6	5.93 (4.3 to 7.56)	4.97 (3.33 to 6.41)	.74	.81
12	7.11 (5.7 to 8.52)	3.98 (2.23 to 5.54)		
18	5.38 (3.28 to 7.48)	3.34 (1.37 to 5.12)		
Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; ANCOVA, analysis of covariance; BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating; CI, confidence interval; MCS, Medical Outcomes 36-Item Short Form (SF-36) mental component summary; PCS, SF-36 physical component summary.				

Participants in the physical activity group also had better delayed recall than those in the usual care group. When the analyses were limited to participants with mild cognitive impairment (**TABLE 3**; post hoc analysis), only the ADAS-Cog scores were significantly different.

Table 3. Effects of the Intervention and Time on Cognitive Outcomes, Mood, and Quality of Life of Participants with Mild Cognitive Impairment Only (Intention-to-Treat Method Using Multiply Imputed Data)

	Mean Difference From Baseline (95% CI)		***P* Value ANCOVA for Repeated Measures**	
	Exercise Group (n = 48)	**Control Group (n = 52)**	**Between Participants**	**Within Participants**
Total ADAS-Cog score				
6	-0.86(-0.98 to 0.69)	0.14 (0.06 to 2.01)	.03	.38
12	-0.62(-1.24 to 0.35)	-0.86 (-0.92 to 0.83)		
18	-0.59(-1.36 to 0.18)	-0.44(-0.52 to 1.07)		
Word list total immediate recall				
6	1.24 (0.33 to 1.92)	0.81 (0.15 to 1.8)	.50	.17
12	1.35 (0.31 to 2.15)	0.97 (0.43 to 2.03)		
18	1.71 (0.79 to 2.38)	0.69 (0.44 to 2.07)		

Word list delayed recall				
6	0.6 (-0.06 to 1.02)	-0.52 (-0.87 to 0.96)	.08	.15
12	0.52 (-0.16 to 0.97)	-1.12 (-1.72 to 0.41)		
18	0.91 (0.32 to 1.25)	-0.92 (-0.42 to 0.51)		
Digit symbol coding total				
6	2.77 (1.06 to 4.23)	2.53 (1.9 to 5.1)	19	.22
12	2.9 (1.22 to 4.33)	2.99 (2.39 to 5.53)		
18	3.87 (2.17 to 5.33)	2.12 (1.41 to 4.75)		
Verbal fluency total score				
6	2.03 (0.11 to 3.87)	-0.47 (-1.3 to 1.88)	.83	.56
12	2.92 (1.19 to 4.35)	-0.02 (-1.15 to 2.21)		
18	2.05 (0.04 to 3.89)	0.52 (-0.92 to 3.48)		
CDR sum of boxes				
6	-0.01 (-0.41 to 0.16)	-0.87 (-0.19 to 0.37)	.04	.07
12	-0.06 (-0.45 to 0.1)	-0.12 (-0.23 to 0.32)		
18	-0.18 (-0.55 to -0.05)	-1.1 (-0.39 to 0.16)		
BDI score				
6	-0.79 (-1.86 to 0.03)	-1.65 (-1.68 to 0.32)	.44	.19
12	-0.6 (-1.71 to 0.27)	-1.34 (-1.35 to 0.59)		
18	-0.31 (-1.56 to 0.7)	-1.41 (-1.5 to 0.61)		
PCS score				
6	-3.89 (-5.8 to -3.22)	-5.3 (-6.16 to -2.51)	.56	.34
12	-4.34 (-6.12 to -2.81)	-4.63 (-5.73 to -1.6)		
18	-4.7 (-6.87 to -2.77)	-5.59(-6.58 to -2.68)		
MCS score				
6	5.28 (3.31 to 7.01)	3.47 (2.67 to 6.2)	.84	.38
12	6.46 (4.71 to 7.97)	2.48 (1.57 to 5.33)		
18	4.73 (2.29 to 6.93)	1.84 (0.71 to 4.91)		

Abbreviations:
ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; ANCOVA, analysis of covariance; BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating; CI, confidence interval; MCS, Medical Outcomes 36-Item Short Form (SF-36) mental component summary; PCS, SF-36 physical component summary.

The complete-case analysis confirmed that participants randomized to the exercise group had better ADAS-Cog scores than those in the usual care control group throughout the trial (**TABLE 4**). They also had significantly better delayed recall and lower Clinical Dementia Rating sum of boxes scores than those in the usual care control group (Table 4).

Table 4. Effects of the Intervention and Time on Cognitive Outcomes, Mood, and Quality of Life of Participants Who Completed All Assessments (Complete-Case Analysis)

	Mean Difference From Baseline (95% CI)		***P* Value ANCOVA for Repeated Measures**	
	Exercise Group (n = 42)	**Control Group (n = 42)**	**Between Participants**	**Within Participants**
Total ADAS-Cog score				
6	0.34 (0.26 to 2.01)	0.93 (-0.58 to 1.91)	.009 (1, 127)	.25 (2, 127)
12	-0.86 (-0.72 to 0.83)	-0.07 (-1.56 to 0.73)		
18	-0.94 (-0.52 to 1.07)	-0.15 (-1.36 to 0.97)		
Word list total immediate recall				
6	0.21 (0.15 to 1.8)	0.8 (-0.69 to 1.7)	.48	.18
12	0.57 (0.43 to 2.03)	1.06(-0.41 to 1.93)		
18	0.59 (0.44 to 2.07)	1.08 (-0.4 to 1.97)		
Word list delayed recall				
6	-0.02 (-0.07 to 0.96)	0.27 (-0.91 to 0.86)	.02	.10
12	-0.12 (-0.72 to 0.41)	-0.33 (-1.56 to 0.31)		
18	-0.22 (-0.42 to 0.51)	-0.13 (-1.26 to 0.41)		
Digit symbol coding total				
6	2.53 (1.9 to 5.1)	3.32 (1.06 to 5)	19	.22
12	2.99 (2.39 to 5.53)	3.78 (1.55 to 5.43)		
18	2.12 (1.41 to 4.75)	2.91 (0.57 to 4.65)		
Verbal fluency total score				
6	-0.47 (-1.3 to 1.88)	0.32(-2.14 to 1.78)	.13	.78
12	-0.02 (-1.15 to 2.21)	0.77 (-1.99 to 2.11)		
18	0.52 (-0.92 to 3.48)	1.31 (-1.76 to 3.38)		
CDR sum of boxes				
6	-0.87 (-0.19 to 0.37)	-0.08 (-1.03 to 0.27)	.05	.04
12	-0.92 (-0.23 to 0.32)	-0.13 (-1.07 to 0.22)		
18	-1.1 (-0.39 to 0.16)	-0.31 (-1.23 to 0.06)		
BDI score				
6	-1.65 (-1.68 to 0.32)	-0.86 (-2.52 to 0.22)	.37	.14
12	-1.34 (-1.35 to 0.59)	-0.55 (-2.19 to 0.49)		
18	-1.41 (-1.5 to 0.61)	-0.62 (-2.34 to 0.51)		
PCS score				
6	-5.3 (-6.16 to -2.51)	-4.51 (-7 to -2.61)	.78	.49
12	-4.63 (-5.73 to -1.6)	-3.84 (-6.57 to -1.7)		
18	-5.59 (-6.58 to -2.68)	-4.8 (-7.42 to -2.78)		
MCS score				
6	3.47 (2.67 to 6.2)	4.26 (1.83 to 6.1)	.52	.64
12	2.48 (1.57 to 5.33)	3.27 (0.73 to 5.23)		
18	1.84 (0.71 to 4.91)	2.63 (-0.13 to 4.81)		

Abbreviations:
ADAS-Cog, Alzheimer Disease Assessment Scale–Cognitive Subscale; ANCOVA, analysis of variance; BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating; CI, confidence interval; MCS, Medical Outcomes 36-Item Short Form (SF-36) mental component summary; PCS, SF-36 physical component summary.

TABLE 5 shows changes in physical activity measures throughout the trial according to group membership. As expected, participants in the physical activity group increased their level of physical activity compared with usual care controls. At 6 months, participants in the physical activity group were walking about 8000 steps a week more than the usual care control group due to both an increase in steps in the group and a decrease in the control group. This difference between the groups, respectively, remained relatively stable at 12 months, but decreased to approximately 6000 steps per week by 18 months. There was a non-significant trend for participants in the physical activity group to spend more time in moderate-plus activities than usual care controls. We also examined the proportion of people in each group who achieved the equivalent of 70 000 steps or more per week at each time point (complete-case analysis only). At 6 months, 9 of 55 participants (16.0%) in the physical activity and 7 of 55 participants (12.7%) in the usual care control groups reached the target number of steps. At 12 months, 16 of 25 (29.0%) in the physical activity and 11 of 55 (20.0%) in the usual care groups reached target (*P*=.08), and at 18 months the proportion reaching the target number of steps was 8 of 55 (14.5%) for both groups (P.89).

Table 5. Effects of the Intervention on Objective Measures of Physical Activity Relative to Baseline (Intention-to-Treat Analysis Using Multiply Imputed Data)

Measure, mo	**Mean Difference From Baseline (95% CI)**		***P* Value ANCOVA for Repeated Measures**	
	Exercise Group (n = 28)	**Control Group (n = 30)**	**Between Participants**	**Within Participants**
Total steps per week				
6	4284.73 (615.21 to 8268.26)	-4843.38 (-6835.3 to 427.16)	.08	.84
12	7342.34 (4621.18 to 11 425)	-668.74 (-3749.74 to 2964.99)		
18	2160.32 (-1116.52 to 6279.84)	-2374.68 (-7264.53 to 1191.85)		
All moderate-intensity-plus activities c				
6	86.09 (47.42 to 149.77)	-58.91(-140.21to 9.61)	.06	.08
12	-8.20 (-54.40 to 29.00)	-51.17 (-130.49 to 16.84)		
18	-8.56 (-43.88 to 46.23)	-41.19 (-117.5 to 19.88)		
All moderate-intensity–related activities				
6	160.45 (84.03 to 190.87)	-69.38 (-173.01 to 6.77)	.02	.10
12	44.37 (-38.07 to 91.82)	-90.22 (-115.66 to -24.22)		
18	55.76 (-46.41 to 1.10)	-115.02 (-190.36 to -86.32)		
Energy expended in all moderate-plus activities, kcal				
6	264.62 (84.15 to 538.08)	-83.43 (-263.96 to 4.91)	.14	.27
12	72.75 (-191.31 to	-143.89 (-212.45 to		

	411.18)	165.34)		
18	63.72 (-142.26 to 315.18)	-43.02 (-91.47 to 363.56)		
Abbreviation: ANCOVA, analysis of covariance; CI, confidence interval.				

8. COMMENT

The trail tried to demonstrate that exercise improves cognitive function in older adults with subjective and objective mild cognitive impairment. The benefits of physical activity were apparent after 6 months and persisted for at least another 12 months after the intervention had been discontinued. The average improvement of 0.34 points on the ADAS-Cog score compared with the usual care control group at 18 months is small but potentially important when one considers the relatively modest amount of physical activity undertaken by participants in the study.

The study intervention resulted in 132 minutes more physical activity per week or 18.8 minutes per day than with usual care. Unlike medication, which was found to have no significant effect on mild cognitive impairment at 36 months, physical activity has the advantage of health benefits that are not confined to cognitive function alone, as suggested by findings on depression, quality of life, falls, cardiovascular function, and disability.

In our study, participants in the intervention group improved 1.1 points on the ADAS-Cog relative to the usual care control group after 6 months. This result compares favorably with the reported improvement of 0.5 points associated with the use of donepezil. Importantly, the beneficial effects of physical activity were sustained, albeit attenuated, during the 18-month follow-up period (mean difference of 0.34 points on the ADAS-Cog) vs the nonsignificant difference of 0.14 points associated with the use of donepezil at 18 months. Importantly, the ADASCog results remained largely unchanged when only people meeting criteria for the diagnosis of mild cognitive impairment were included in the analyses, suggesting that our sampling strategy cannot explain our findings (ie, they were not due to the inclusion of people with subjective memory complaints but no objective cognitive impairment).

The mechanisms by which physical activity improves cognition in older people at increased risk of dementia are not clear. One possible mechanism is an alteration in cerebral vascular functioning and brain perfusion. Studies involving animal models have shown that physical activity can stimulate angiogenesis, brain perfusion and neurovascular integrity within 3 to 4 weeks.

Another possible mechanism is environment enrichment associated with greater physical activity. Basic research has shown that enriched environments are activity prone and contribute to enhanced brain plasticity via synaptogenesis, neurogenesis, and attenuation of neural responses to stress. For example, Uda et al 49 compared the hippocampus of control adult rats with rats that ran on a treadmill for 30-minute a day for 7 days.

Active rats had more astrocytes and neuroblasts with proliferative ability in the sub granular zone of the dentate gyrus of the hippocampus, as well as increased number of neurons in transient stage than control rats. The authors speculated that the observed changes were associated with increased production of fibroblast growth factor 2 in the active rats.

Likewise, Kronenberg et al demonstrated in a mouse model that voluntary wheel running induced neurogenesisin older animals. They suggested that this effect was partly mediated by *N*methyl-D-asparte receptors, a shift in corticoid receptor expression in the hippocampus, and activation of insulin like growth factor 1, vascular endothelial growth factor, brain-derived neurotrophic factor, and endorphins.

In humans, Colcombe et al demonstrated that physical activity is associated with increased blood perfusion of brain regions that modulate attention. Twenty-nine high-functioning older adults were randomly assigned to either aerobic activity or stretching and toning activity. The aim of the aerobic exercise group was to improve cardiorespiratory fitness, whereas the stretching and toning group served as a control group. Participants in both groups met 3 times a week for 40 to 45 minutes. After 6 months, participants in the aerobic exercise group showed a significantly greater task-related activity in attentional control areas, such as the middle frontal gyrus, the superior frontal gyrus, and the superior parietal lobule.50 The authors suggested that the increased activity was due to physical activity stimulated synaptogenesis, increased blood supply, and unspecified cholinergic effects.
Clinical evidence suggests that physical activity increases well-being, as demonstrated by a meta-analysis of 36 physical activity studies of older adults. 40 The results of our trial failed to show a significant effect of physical activity on mood and quality of life, which suggests that improved well-being is unlikely to have confounded our results.

The observed interaction between physical activity and *APOE ε* 4 genotype is of interest, albeit post hoc. *APOE ε*4 carriers show metabolic and structural changes in brain areas known to be affected in people with AD well before the development of clinically manifest cognitive impairment. Therefore, it is possible that the cognitive benefits associated with physical activity in this trial were attenuated by preexisting or ongoing deleterious effects of *APOE ε*4 .

This trial has limitations. The study sample was relatively young and may not represent well the population at highest risk of cognitive decline. In addition, this was a single-site trial of motivated volunteers from the community who were free of significant medical morbidities and dementia and, consequently, the results may not be readily transferable to a clinical population. In addition, the study had no access to brain imaging or biochemistry, so that the potential physiological mechanisms mediating the relationship between physical activity and cognitive function could not be identified. The neuropsychological battery used to assess participants was limited to a general measure of cognitive function (ADAS-Cog), verbal memory and fluency, and digit-symbol substitution.

As a result, we were unable to determine whether specific cognitive skills are more amenable to the changes associated with physical activity than others. Furthermore, the

effect size of the intervention was small and, while it supports the concept that physical activity can reduce the rate of cognitive decline, the clinical significance of our findings remains to be established.

Finally, the results of this trial cannot be used to infer that physical activity reduces the risk of dementia among at risk older adults, because the study was not powered to investigate development of dementia.

An important merit of this trial was to demonstrate the potential benefit of a simple intervention that is almost universally available. The intervention was based on the stages of change model that has been shown to be effective in increasing and maintaining physical activity in older adults. Strategies used included individually tailored programs, giving feedback about progress, and increasing participants' perceived benefits of being more physically active. The program was safe and had good adherence.

In summary, the results of this randomized trial indicate that a physical activity program of an additional 142 minutes of exercise per week on average modestly improved cognition relative to controls in older adults with subjective and objective memory impairment.

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