

# Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease

## A Randomized Trial

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**A**S THE WORLD POPULATION ages, the number of older adults living with Alzheimer disease (AD) is estimated to increase from the current 26.6 million to 106.2 million by 2050.<sup>1</sup> If illness onset could be delayed by 12 months, 9.2 million fewer cases of AD would occur worldwide.<sup>1</sup> For this reason, attempts have been made to identify individuals who are at increased risk of AD and to test interventions that might delay the progression of prodromal symptoms to full-blown dementia. The results from observational studies suggest that older people who are free of dementia but report memory decline or show objective evidence of cognitive impairment are more likely to develop AD over time.<sup>2,3</sup>

Seven clinical trials have investigated whether cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), vitamin E, piracetam, and rofecoxib (a cyclooxygenase 2 inhibitor) can prevent cognitive decline and progression to dementia in older adults with mild cognitive impairment. In a trial by Petersen et al,<sup>4</sup> 769 participants with mild

**Context** Many observational studies have shown that physical activity reduces the risk of cognitive decline; however, evidence from randomized trials is lacking.

**Objective** To determine whether physical activity reduces the rate of cognitive decline among older adults at risk.

**Design and Setting** Randomized controlled trial of a 24-week physical activity intervention conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Assessors of cognitive function were blinded to group membership.

**Participants** We recruited volunteers who reported memory problems but did not meet criteria for dementia. Three hundred eleven individuals aged 50 years or older were screened for eligibility, 89 were not eligible, and 52 refused to participate. A total of 170 participants were randomized and 138 participants completed the 18-month assessment.

**Intervention** Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity.

**Main Outcome Measure** Change in Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores (possible range, 0-70) over 18 months.

**Results** In an intent-to-treat analysis, participants in the intervention group improved 0.26 points (95% confidence interval, -0.89 to 0.54) and those in the usual care group deteriorated 1.04 points (95% confidence interval, 0.32 to 1.82) on the ADAS-Cog at the end of the intervention. The absolute difference of the outcome measure between the intervention and control groups was -1.3 points (95% confidence interval, -2.38 to -0.22) at the end of the intervention. At 18 months, participants in the intervention group improved 0.73 points (95% confidence interval, -1.27 to 0.03) on the ADAS-Cog, and those in the usual care group improved 0.04 points (95% confidence interval, -0.46 to 0.88). Word list delayed recall and Clinical Dementia Rating sum of boxes improved modestly as well, whereas word list total immediate recall, digit symbol coding, verbal fluency, Beck depression score, and Medical Outcomes 36-Item Short-Form physical and mental component summaries did not change significantly.

**Conclusions** In this study of adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up period.

**Trial Registration** anzctr.org.au Identifier: ACTRN12605000136606

JAMA. 2008;300(9):1027-1037

www.jama.com

cognitive impairment were randomly assigned to receive 10 mg of donepezil, 2000 IU of vitamin E, or placebo daily for 36 months. By study end, progres-

sion to dementia and change in cognitive score did not differ by treatment group. A study of rivastigmine to prevent conversion from mild cognitive

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**See also p 1077 and Patient Page.**

impairment to dementia over 4 years reported similarly negative findings.<sup>5</sup> Preliminary results from 2 galantamine trials that have yet to be completed were also negative,<sup>6</sup> as were the findings from the piracetam<sup>6</sup> and rofecoxib trials.<sup>7</sup> Other strategies to prevent cognitive decline and dementia in people at risk are currently being tested, but available results have been mixed for B vitamins,<sup>8,9</sup> statins,<sup>10</sup> and antihypertensive therapy.<sup>11,12</sup>

Numerous observational studies have found that people who are physically active seem less likely than sedentary persons to experience cognitive decline and dementia in later life. Weuve et al<sup>13</sup> reported that higher levels of physical activity over 2 years among the 18 766 women in the Nurses' Health Study were associated with improved cognitive scores. Similarly, Abbott et al<sup>14</sup> reported that men who walk at least 2 miles a day are 1.8 times less likely than sedentary men to develop dementia over a follow-up period of 6 years. Subsequent prospective studies confirmed that physical activity is associated with reduced incidence of dementia<sup>15,16</sup> and showed that the association of physical activity and cognitive function is apparent even when exercise is limited to later life.<sup>17</sup> However, confirmatory evidence from randomized trials is still lacking.

We designed the present randomized trial to test whether a 24-week home-based physical activity intervention reduces the rate of cognitive decline among older adults at increased risk of dementia.

## METHODS

### Participants

The Fitness for the Aging Brain Study (FABS) was a single-site randomized controlled trial conducted between May 2004 and January 2007 at the Royal Perth Hospital, Australia. Participants were recruited between May 2004 and July 2006 from various sources, including advertisement in the local media and 2 memory clinics.

Volunteers aged 50 years or older were screened with the Telephone Interview for Cognitive Status–Modified. Those with scores lower than 19 of 50 were ex-

cluded due to evidence of significant cognitive impairment.<sup>18</sup> Likewise, individuals with a Geriatric Depression Scale-15<sup>19</sup> score of 6 or higher were excluded from the study due to the presence of clinically significant depressive symptoms. Also excluded were those who reported regularly drinking more than 4 standard units of alcohol a day; had a chronic mental illness, such as schizophrenia; or had medical conditions likely to compromise survival, such as metastatic cancer, or render them unable to engage in physical activity, such as severe cardiac failure. Other exclusion criteria included severe sensory impairment or lack of fluency in written or spoken English.

Potentially eligible participants were invited to an in-person assessment that included the Mini-Mental State Examination,<sup>20</sup> the *International Statistical Classification of Diseases, 10th Revision (ICD-10)*, Clinical Dementia Rating,<sup>21</sup> and the Cognitive Battery of the Consortium to Establish a Registry for Alzheimer Disease.<sup>22</sup> Individuals meeting ICD-10 research criteria for the diagnosis of dementia<sup>23</sup> were excluded from further participation, as were those with a Mini-Mental State Examination score of less than 24, a Clinical Dementia Rating scale score of 1 or more, or who were unable to walk for 6 minutes without assistance.

Volunteers were eligible for randomization if they answered yes to the question: "Do you have any difficulty with your memory?" independent of whether they showed evidence of objective cognitive impairment. Participants were considered to have mild cognitive impairment if their scores were 1.5 SDs or lower than the mean Cognitive Battery of the Consortium to Establish a Registry for Alzheimer's Disease control group scores for their age and sex<sup>24</sup> on the subtests for verbal fluency, object picture naming, word list immediate and delayed recall, and praxis. Eligible participants were also required to obtain consent from their family physician to take part in a physical activity intervention.

The human research ethics committees of the University of Western Australia and of the Royal Perth Hospital ap-

proved this study, and all participants provided written informed consent.

### Assessment of Physical Activity

We used the Community Healthy Activities Program for Seniors (CHAMPS) survey to assess physical activity.<sup>25</sup> Participants were asked to complete the CHAMPS questionnaire twice 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 following summary measures. Physical activity measures included minutes per week spent on 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-Walker SW-700, Yamax Inc, 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.<sup>26</sup> Participants recorded this information in a diary, in which information about when the pedometer was on or off was also registered. When participants performed nonstep 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.<sup>27</sup> Because 10 000 steps per day are associated with improved health outcomes,<sup>28</sup> participants with a weekly step count greater than or equal to 70 000 were classified as *active* and the remainder, *nonactive*.

### 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.<sup>29</sup> The scale consists of 11 brief cognitive tests assessing memory, language, and praxis. Scores range from 0 to 70, 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),<sup>30</sup> 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-Kaplan Executive Function Battery.<sup>31</sup> Participants were also rated according to the Clinical Dementia Rating sum of boxes at each assessment. Premorbid IQ was measured with the Cambridge Contextual Reading Test.<sup>32</sup> 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),<sup>33</sup> 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).<sup>34</sup>

### Apolipoprotein Genotype

We determined apolipoprotein (*APOE*) genotype using standard procedures previously described.<sup>35</sup>

### 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 su-

perision. 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. We are not aware of any breaches of protocol during the course of the trial.

### Usual Care 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.

### 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,<sup>36</sup> which participants were asked to complete in three 50-minute sessions each week. The regimen of 3 sessions a 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 chose activities that required classes or a center venue.<sup>36</sup> 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 other 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.

### Behavioral Intervention

To enhance adherence to the program, participants also received a modified behavioral intervention package based on social cognitive theory.<sup>37</sup> 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 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 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.)

### 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 of-

ferred except for 4 newsletters, as described above.

### 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 dif-

ference considered to be clinically meaningful in clinical treatment trials.<sup>38</sup> The participation of 84 volunteers in each of the 2 groups (n=168) at baseline resulted in power of 90% with  $\alpha$  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).

### Analysis of the Data

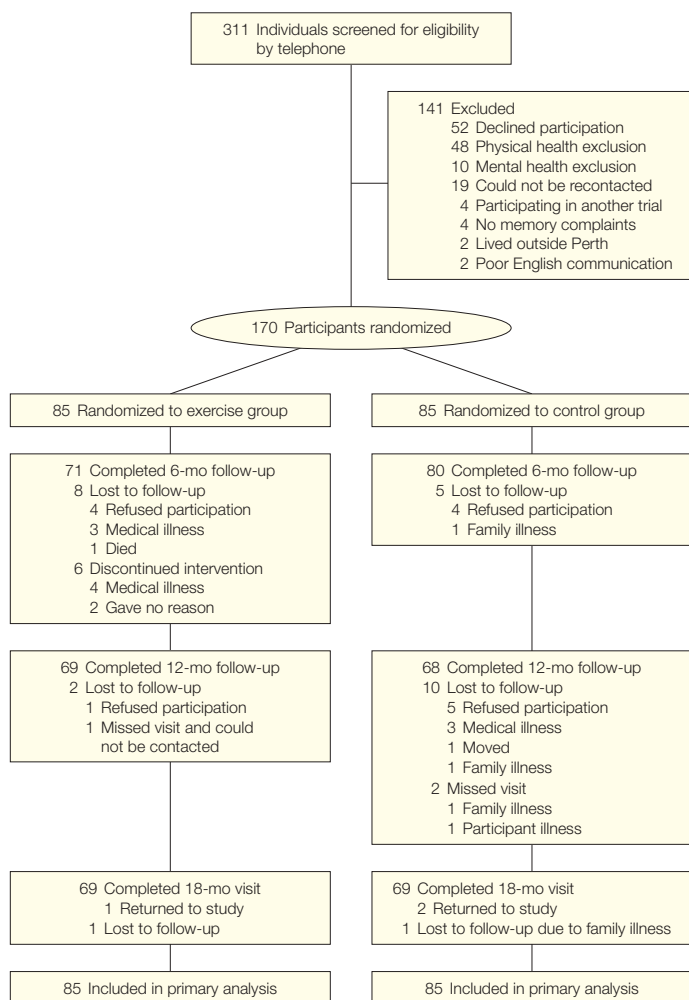
The data were analyzed using the SAS for Windows version 9.1 (SAS Institute Inc, Cary, North Carolina) and SPSS 15.0 for Windows (SPSS Inc, Chicago, Illinois). For normally distributed continuous variables, arithmetic means and SDs were calculated. For logarithmically trans-

formed 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  $\chi^2$ . 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 over time) 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

**Figure.** Flow of Participants From Screening to Completion of the Final Follow-up Assessment



The number of completed cases may vary according to the end point because of missing 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  $\alpha=.05$  was considered statistically significant.

## RESULTS

Three hundred eleven individuals were screened for eligibility over the telephone. The FIGURE shows the flow of participants from the time of screening through study completion at 18 months. One hundred seventy older adults met criteria and consented to take part in the trial, of whom 59 had amnesic mild cognitive impairment single domain; 28, amnesic mild cognitive impairment multiple domain; and 15, nonamnesic mild cognitive impairment.<sup>3</sup> TABLE 1 shows their demographic and clinical characteristics.

### 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 ( $P=.04$ ). 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. 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 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 9000 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 nonsignificant trend for participants in the physical activity group to spend more time in moderate-plus activities than usual care controls. Adherence to the prescribed physical activity for the 24 weeks was 78.2%. 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, 22 of 85 participants (25.0%) in the physical activity and 15 of 85 participants (17.6%) in the usual care control groups reached the target number of steps ( $\chi^2=1.69$ ;  $P=.19$ ). At 12

**Table 1.** Baseline Characteristics of Trial Participants

	Exercise (n = 85)	Control (n = 85)
Age, mean (SD), y	68.6 (8.7)	68.7 (8.5)
Women, No. (%)	42 (49.4)	44 (51.8)
Educational level, mean (SD), y	12.1 (3.4)	12.6 (3.2)
Married or de facto, No. (%)	58 (68.2)	61 (71.8)
Risk factors, No. (%)		
Ever heavy smoker <sup>a</sup>	21 (24.7)	21 (24.7)
Current smoker	1 (1.2)	1 (1.2)
Heart disease	8 (9.4)	10 (11.8)
Hypertension	30 (35.3)	30 (35.3)
Arthritis	41 (48.2)	33 (38.8)
Asthma	18 (21)	20 (23.5)
Health and mental health score, mean (SD)		
BDI	3.6 (3.5)	4.1 (2.8)
PCS	48.5 (9.4)	49.4 (8.7)
MCS	48.4 (7.0)	48.1 (5.5)
All moderate-intensity plus activities, mean (SD), min/wk	126.4 (6.1)	177.2 (5.0)
Total steps/wk, mean (SD)	55 366 (31 353)	57 254 (26 361)
Active participants: reached target steps/wk, No. (%)	21 (24.7)	26 (30.6)
Premorbid IQ, mean (SD)	115.3 (5.0)	116.1 (5.8)
Assessment score, mean (SD)		
ADAS-Cog	7.0 (1.7)	7.0 (1.8)
Word list total immediate recall	18.4 (4.9)	17.4 (4.7)
Word list delayed recall	5.8 (2.6)	5.5 (2.4)
Digit symbol coding	54.2 (15.1)	53.4 (14.1)
Verbal fluency total score	37.8 (11.5)	39.5 (13.1)
CDR sum of boxes	1.0 (0.7)	1.0 (0.7)
APOE $\epsilon 4$ carrier, No. (%)	24 (28.2)	27 (31.8)
Clinical subtype, No. (%)		
Subjective memory complaints only	37 (43.5)	31 (36.5)
Amnesic MCI	38 (44.7)	47 (55.3)
Nonamnesic MCI	10 (11.8)	7 (8.2)

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.

<sup>a</sup>More than 20 cigarettes a day for a year or more.

months, 25 of 85 (29.4%) in the physical activity and 15 of 85 (17.6%) in the usual care groups reached target ( $\chi^2=3.27; P=.07$ ), and at 18 months the proportion reaching the target number of steps was 16 of 85 (18.8%) for both groups ( $\chi^2=0; P>.99$ ).

Adverse events were defined as any physical or psychological symptoms that occurred any time after randomization and led to exclusion of the participant from further participation or re-

quired the participant to interrupt the study temporarily. Ten events occurred during the study and intervention staff judged that it was unlikely any of these events were directly caused by the intervention (TABLE 6).

We conducted a series of post hoc analyses to determine whether the observed differences between physical activity and usual care control groups could be explained by differential loss to follow-up. Women were more likely

than men to drop out in both groups, and those who dropped out had higher ADAS-Cog scores than those who remained in the trial (TABLE 7).

We also completed a series of post hoc analyses to clarify whether treatment response was associated with APOE genotype. Fifty-one study participants (30%) carried at least 1 APOE  $\epsilon 4$  allele (24 in the physical activity and 27 in the usual care control group). In a complete-case analysis of 18 months, there was a dif-

**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)<sup>a</sup>

Measure, mo	Mean Difference From Baseline (95% CI)		P Value ANCOVA for Repeated Measures <sup>b</sup>	
	Exercise Group (n = 85)	Control Group (n = 85)	Between Participants	Within Participants
Total ADAS-Cog score				
6	-0.26 (-0.89 to 0.54)	1.04 (0.32 to 1.82)	.04	.54
12	-0.55 (-1.15 to 0.20)	0.04 (-0.66 to 0.64)		
18	-0.73 (-1.27 to 0.03)	-0.04 (-0.46 to 0.88)		
Word list total immediate recall				
6	1.09 (0.42 to 1.77)	0.91 (0.21 to 1.61)	.48	.18
12	1.20 (0.40 to 2.00)	1.17 (0.49 to 1.84)		
18	1.56 (0.88 to 2.23)	1.19 (0.5 to 1.88)		
Word list delayed recall				
6	0.45 (0.03 to 0.87)	0.38 (-0.01 to 0.77)	.02	.10
12	0.37 (-0.07 to 0.82)	-0.22 (-0.66 to 0.22)		
18	0.76 (0.41 to 1.10)	-0.02 (-0.36 to 0.32)		
Digit symbol coding total				
6	2.62 (1.15 to 4.08)	3.43 (1.96 to 4.91)	.19	.22
12	2.75 (1.31 to 4.18)	3.89 (2.45 to 5.34)		
18	3.72 (2.26 to 5.18)	3.02 (1.47 to 4.56)		
Verbal fluency total score				
6	1.88 (0.20 to 3.72)	0.43 (-1.24 to 1.69)	.13	.78
12	2.77 (1.28 to 4.28)	0.88 (-1.09 to 2.02)		
18	1.90 (0.13 to 3.74)	1.42 (-0.86 to 3.29)		
CDR sum of boxes				
6	-0.16 (-0.32 to 0.01)	0.03 (-0.13 to 0.18)	.05	.05
12	-0.21 (-0.36 to -0.05)	-0.02 (-0.17 to 0.13)		
18	-0.33 (-0.46 to -0.2)	-0.20 (-0.33 to -0.03)		
BDI score				
6	-0.94 (-1.77 to -0.12)	-0.75 (-1.62 to 0.13)	.44	.19
12	-0.75 (-1.62 to 0.12)	-0.44 (-1.29 to 0.40)		
18	-0.46 (-1.47 to 0.55)	-0.51 (-1.44 to 0.42)		
PCS score				
6	-4.04 (-5.71 to -2.37)	-4.40 (-6.1 to -2.70)	.95	.39
12	-4.49 (-6.03 to -2.96)	-3.73 (-5.67 to -1.79)		
18	-4.85 (-6.78 to -2.92)	-4.69 (-6.52 to -2.87)		
MCS score				
6	5.13 (3.40 to 6.86)	4.37 (2.73 to 6.01)	.67	.79
12	6.31 (4.80 to 7.82)	3.38 (1.63 to 5.14)		
18	4.58 (2.38 to 6.78)	2.74 (0.77 to 4.72)		

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.

<sup>a</sup>Mixed-effect models with repeated measures and analysis of variance F tests used. Covariates including age, sex, educational level, premorbid IQ, marital status, and baseline measure adjusted.

<sup>b</sup>Degrees of freedom for between-participant and within-participant analyses are (1,162) and (2,162), respectively. The first degree of freedom in parentheses refers to that for effect (between groups or between times) and the second to that for the error term.

ferential effect of exercise on ADAS-Cog scores according to *APOE*  $\epsilon 4$  carrier status, with the change in ADAS-Cog scores across the course of the study for *APOE*  $\epsilon 4$  noncarriers in the physical activity group being significantly better than scores of individuals in the other groups combined ( $F_1=8.73$ ;  $P=.004$ ). The ADAS-Cog scores among *APOE*  $\epsilon 4$  noncarriers in the physical activity group differed from *APOE*  $\epsilon 4$  carriers and noncarriers in the usual care control group

( $F_1=4.59$ ;  $P=.04$  and  $F_1=5.011$ ;  $P=.03$ , respectively). There were no other significant between-participant differences.

### COMMENT

To our knowledge, this trial is the first 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 0.69 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 142 minutes more physical activity per week or 20 minutes per day than with usual care. Unlike medication, which was

**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)<sup>a</sup>

Measure, mo	Mean Difference From Baseline (95% CI)		P Value ANCOVA for Repeated Measures <sup>b</sup>	
	Exercise Group (n = 48)	Control Group (n = 52)	Between Participants	Within Participants
Total ADAS-Cog score				
6	-0.87 (-1.83 to 0.08)	1.29 (0.20 to 2.39)	.02	.45
12	-0.39 (-1.39 to 0.61)	0.02 (-0.79 to 0.83)		
18	-0.38 (-1.39 to 0.63)	0.45 (-0.46 to 1.36)		
Word list total immediate recall				
6	0.77 (0.15 to 1.39)	0.25 (-0.26 to 0.76)	.15	.39
12	0.75 (0.11 to 1.39)	-0.46 (-0.9 to -0.01)		
18	0.92 (0.45 to 1.38)	-0.22 (-0.64 to 0.21)		
Word list delayed recall				
6	1.83 (0.89 to 2.78)	1.46 (0.57 to 2.34)	.48	.55
12	1.48 (0.30 to 2.66)	1.55 (0.57 to 2.53)		
18	1.4 (0.41 to 2.39)	1.42 (0.48 to 2.37)		
Digit symbol coding total				
6	2.06 (-0.04 to 4.17)	2.23 (0.63 to 3.84)	.50	.22
12	3.10 (1.01 to 5.19)	3.48 (1.70 to 5.27)		
18	3.43 (1.57 to 5.29)	2.23 (0.20 to 4.26)		
Verbal fluency total score				
6	0.25 (-0.35 to 1.5)	1.18 (0.14 to 1.87)	.77	.73
12	0.75 (0.08 to 1.77)	2.45 (1.47 to 3.19)		
18	-0.33 (-1.03 to 0.70)	2.66 (1.24 to 3.66)		
CDR sum of boxes				
6	-0.24 (-0.47 to 0.00)	0.00 (-0.22 to 0.24)	.19	.22
12	-0.33 (-0.53 to -0.08)	0.01 (-0.20 to 0.27)		
18	-0.41 (-0.62 to -0.25)	-0.17 (-0.47 to -0.02)		
BDI score				
6	-0.73 (-1.78 to 0.32)	-0.29 (-1.48 to 0.90)	.59	.34
12	-0.40 (-1.67 to 0.87)	-0.06 (-1.21 to 1.08)		
18	-0.22 (-1.67 to 1.24)	-0.09 (-1.38 to 1.20)		
PCS score				
6	-3.47 (-5.89 to -1.04)	-5.43 (-7.64 to -3.21)	.56	.70
12	-4.94 (-6.75 to -3.14)	-2.99 (-5.04 to -0.93)		
18	-3.97 (-6.76 to -1.19)	-3.49 (-5.85 to -1.12)		
MCS score				
6	4.80 (2.46 to 7.13)	4.77 (2.38 to 7.15)	.88	.89
12	6.31 (4.03 to 8.58)	3.86 (1.65 to 6.06)		
18	3.94 (0.61 to 7.26)	3.10 (0.06 to 6.14)		

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.

<sup>a</sup>Mixed effect models with repeated measures and analysis of variance *F* tests used. Covariates including age, sex, educational level, premorbid IQ, marital status, and baseline measure adjusted.

<sup>b</sup>Degrees of freedom for between-participant and within-participant analyses are (1,92) and (2,92), respectively. The first degree of freedom in parentheses refers to that for effect (between groups or between times) and the second to that for the error term.

found to have no significant effect on mild cognitive impairment at 36 months,<sup>39</sup> physical activity has the advantage of health benefits that are not confined to cognitive function alone, as suggested by findings on depression,<sup>40</sup> quality of life,<sup>41</sup> falls,<sup>42</sup> cardiovascular function,<sup>43</sup> and disability.<sup>44</sup>

In our study, participants in the intervention group improved 1.3 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.<sup>4</sup> Importantly, the beneficial effects of physical activity were sustained, albeit attenuated, during the 18-month follow-up period (mean difference of 0.69 points on the ADAS-Cog) vs the

nonsignificant difference of 0.2 points associated with the use of donepezil at 18 months.<sup>4</sup> Importantly, the ADAS-Cog 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

**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)<sup>a</sup>

Measure, mo	Mean Difference From Baseline (95% CI)		P Value (Degree of Freedom) ANCOVA for Repeated Measures <sup>b</sup>	
	Exercise Group (n = 69)	Control Group (n = 69)	Between Participants	Within Participants
Total ADAS-Cog score <sup>c</sup>				
6	-0.50 (-1.26 to 0.26)	0.79 (0.03 to 1.55)	.009 (1, 127)	.25 (2, 127)
12	-0.49 (-1.24 to 0.26)	0.41 (-0.21 to 1.03)		
18	-0.61 (-1.34 to 0.12)	0.5 (-0.14 to 1.14)		
Word list total immediate recall <sup>c</sup>				
6	1.12 (0.40 to 1.83)	0.58 (-0.15 to 1.30)	.09 (1, 127)	.51 (2, 127)
12	1.28 (0.37 to 2.18)	0.91 (0.16 to 1.65)		
18	1.65 (0.90 to 2.39)	1.18 (0.42 to 1.93)		
Word list delayed recall <sup>c</sup>				
6	0.51 (0.05 to 0.97)	0.42 (0.02 to 0.82)	.01 (1, 127)	.45 (2, 127)
12	0.60 (0.15 to 1.05)	-0.27 (-0.77 to 0.23)		
18	0.88 (0.51 to 1.25)	0.00 (-0.38 to 0.38)		
Digit symbol coding total <sup>d</sup>				
6	2.06 (0.48 to 3.64)	3.86 (2.32 to 5.40)	.43 (1, 126)	.77 (2, 126)
12	2.81 (1.15 to 4.47)	4.29 (2.64 to 5.94)		
18	3.62 (1.91 to 5.33)	3.38 (1.60 to 5.15)		
Verbal fluency total score <sup>c</sup>				
6	2.31 (0.29 to 4.33)	0.42 (-1.09 to 1.93)	.07 (1, 127)	.88 (2, 127)
12	3.00 (1.26 to 4.74)	0.78 (-0.95 to 2.51)		
18	2.54 (0.48 to 4.60)	0.99 (-1.39 to 3.37)		
CDR sum of boxes <sup>d</sup>				
6	-0.25 (-0.43 to -0.07)	0.04 (-0.12 to 0.20)	.003 (1, 126)	.64 (2, 126)
12	-0.26 (-0.43 to -0.09)	-0.05 (-0.22 to 0.12)		
18	-0.36 (-0.50 to -0.22)	-0.19 (-0.36 to -0.02)		
BDI score <sup>d</sup>				
6	-0.88 (-1.79 to 0.03)	-0.40 (-1.32 to 0.52)	.35 (1, 126)	.77 (2, 126)
12	-0.74 (-1.66 to 0.18)	-0.14 (-1.10 to 0.82)		
18	-0.40 (-1.55 to 0.75)	-0.27 (-1.27 to 0.73)		
PCS score <sup>e</sup>				
6	-4.05 (-5.91 to -2.19)	-4.13 (-5.89 to -2.37)	.75 (1, 125)	.08 (2, 125)
12	-4.29 (-6.02 to -2.56)	-3.83 (-6.02 to -1.64)		
18	-4.83 (-7.10 to -2.56)	-4.30 (-6.17 to -2.43)		
MCS score <sup>e</sup>				
6	5.44 (3.51 to 7.37)	4.14 (2.42 to 5.86)	.08 (1, 125)	.37 (2, 125)
12	6.20 (4.49 to 7.91)	3.21 (1.20 to 5.22)		
18	4.67 (2.07 to 7.27)	2.90 (0.71 to 5.09)		

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.

<sup>a</sup>Repeated measures ANCOVA analysis and analysis of variance *F* tests used. Covariates including age, sex, education level, premorbid IQ, marital status, and baseline measure adjusted. The number of completed cases may vary according to the end point because of missing data.

<sup>b</sup>The first degree of freedom in parentheses refers to that for effect (between groups or between times) and the second to that for the error term.

<sup>c</sup>Data were available for 68 participants in the exercise group and 67 in the control group.

<sup>d</sup>Data were available for 68 participants in the exercise group and for 66 in the control group.

<sup>e</sup>Data were available for 66 participants in the exercise group and 67 in the control group.

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

Measure, mo	Mean Difference From Baseline (95% CI)		P Value ANCOVA for Repeated Measures <sup>b</sup>	
	Exercise Group (n = 85)	Control Group (n = 85)	Between Participants	Within Participants
Total steps per week				
6	5207.48 (513.51 to 9208.46)	-4024.91 (-8760.7 to 302.14)	.009	.78
12	8947.74 (3787.37 to 14 529)	-564.03 (-5735.65 to 3599.74)		
18	3290.70 (-1231.22 to 7999.36)	-2989.68 (-8739.04 to 2161.33)		
All moderate-intensity-plus activities <sup>c</sup>				
6	95.55 (23.59 to 167.51)	-46.57 (-110.59 to 17.45)	.09	.02
12	-9.79 (-66.89 to 47.32)	-61.71 (-134.45 to 11.03)		
18	-6.68 (-68.27 to 54.9)	-48.58 (-118.39 to 21.23)		
All moderate-intensity-related activities				
6	173.44 (76.48 to 270.41)	-80.16 (-165.23 to 4.92)	.12	.02
12	31.60 (-55.09 to 118.29)	-107.17 (-196.72 to -17.63)		
18	53.06 (-36.28 to 142.39)	-129.89 (-224.56 to -35.22)		
Energy expended in all moderate-plus activities, kcal				
6	419.48 (86.26 to 752.69)	-98.09 (-413.82 to 217.64)	.12	.05
12	57.39 (-206.55 to 321.33)	-145.36 (-456.64 to 165.92)		
18	39.39 (-255.61 to 334.39)	-47.01 (-324.39 to 230.36)		

Abbreviation: ANCOVA, analysis of covariance; CI, confidence interval.

<sup>a</sup>Mixed effect models with repeated measures and ANOVA *F* tests used. Covariates including age, sex, education level, premorbid IQ, marital status, and baseline measure adjusted.

<sup>b</sup>Degrees of freedom for between-participant and within-participant analyses are (1,162) and (2,162), respectively. The first degree of freedom in parentheses refers to that for effect (between groups or between times) and the second to that for the error term.

<sup>c</sup>Minutes per week of all activities that were moderate, hard, and very hard.

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.<sup>45</sup> Another possible mechanism is environment enrichment associated with greater physical activity.<sup>46</sup> Basic research has shown that enriched environments are activity-prone<sup>46,47</sup> and contribute to enhanced brain plasticity via synaptogenesis, neurogenesis, and attenuation of neural responses to stress.<sup>48,49</sup> For example, Uda et al<sup>49</sup> 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 subgranular 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 as-

**Table 6.** Adverse Events and Discontinuation of Intervention During Active (First 24 Weeks) or After Active (24 Weeks to 18 Months) Period

	Control Group	Intervention Group During Active Phase	Intervention Group After Active Phase
Total adverse events reported	2	3	5
Cardiovascular problem	1	1 <sup>a</sup>	2
Stroke or transient ischemic attack	1	0	1 <sup>d</sup>
Inoperable lung cancer	0	1 <sup>b</sup>	0
Foot pain and gout	0	1 <sup>c</sup>	0
Disorientation episodes	0	0	1
Shoulder operation needing 8-wk recovery	0	0	1 <sup>d</sup>

<sup>a</sup>This event (myocardial infarction) took place before the intervention commenced.

<sup>b</sup>Diagnosed during intervention active phase, illness resulted in loss to 6-month follow-up data (participant died shortly after).

<sup>c</sup>Preexisting gout and foot pain led to temporary interruption in intervention.

<sup>d</sup>These 2 events occurred in the same participant.

sociated with increased production of fibroblast growth factor 2 in the active rats. Likewise, Kronenberg et al<sup>48</sup> demonstrated in a mouse model that voluntary wheel running induced neurogenesis in older animals. They suggested that this effect was partly mediated by *N*-methyl-D-aspartate receptors, a shift in corticoid receptor expression in the hippocampus, and activation of insulinlike growth factor 1, vascular endothelial growth factor, brain-derived neurotrophic factor, and endorphins.

In humans, Colcombe et al<sup>50</sup> 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. Af-

**Table 7.** Demographic and Clinical Characteristics of Participants at Baseline Who Completed and Dropped Out of the Trial<sup>a</sup>

Variable	Exercise Group			Control Group		
	Completers (n = 69)	Dropouts (n = 16)	P Value	Completers (n = 69)	Dropouts (n = 16)	P Value
Women, No. (%)	31 (44.9)	11 (68.7)	.09	32 (46.4)	12 (75.0)	.04
Age, mean (SD), y	68.7 (8.7)	67.9 (9.1)	.73	68.4 (9.0)	69.9 (6.2)	.55
Total education, mean (SD), y	12.1 (3.2)	12.3 (4.6)	.83	12.6 (3.3)	12.7 (2.8)	.90
Married, No. (%) <sup>b</sup>	48 (69.6)	10 (62.5)	.58	48 (69.6)	13 (81.2)	.35
Assessment score, mean (SD)						
BDI total	3.3 (3.7)	5.3 (2.3)	.17	3.9 (2.7)	5.0 (3.3)	.38
Predicted full IQ	115.1 (5.2)	115.9 (4.2)	.56	116.5 (5.8)	114.4 (5.8)	.18
Total ADAS-Cog	7.1 (1.7)	6.8 (1.8)	.79	6.4 (1.8)	10.6 (1.4)	.001
PCS	49.2 (8.9)	45.4 (11.1)	.15	49.6 (8.0)	48.2 (11.4)	.55
MCS	48.5 (7.0)	47.6 (7.5)	.63	48.4 (5.1)	46.9 (6.8)	.33
Reached target of 70 000, steps/wk, No. (%)	16 (23.2)	5 (31.2)	.51	22 (31.9)	4 (25.0)	.59
Steps for the wk NSA adjusted, mean (SD)	54 454.5 (32 105.3)	59 498.8 (28 326.7)	.58	59 195.1 (25 884.4)	49 007.3 (27 619.2)	.17
Moderate intensity plus activities at baseline, mean (SD), min/wk	294.6 (304.2)	182.8 (257.6)	.18	371.1 (338.6)	258.7 (222.2)	.21

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale—Cognitive Subscale; MCS, Medical Outcomes 36-Item Short Form (SF-36) mental component summary; nonstep physical activity NSA, PCS, SF-36 physical component summary.

<sup>a</sup>The number of completed cases may vary according to the end point because of missing data.

<sup>b</sup>De facto included in married group.

ter 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.<sup>50</sup> 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.<sup>40</sup> 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*  $\epsilon 4$  genotype is of interest, albeit post hoc. *APOE*  $\epsilon 4$  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.<sup>51</sup> 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*  $\epsilon 4$ .

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.<sup>37</sup> 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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**Obtained funding:** Lautenschlager, Cox, Flicker, Foster, Almeida.

**Administrative, technical, or material support:** Lautenschlager, Cox, Flicker, van Bockxmeer, Greenop, Almeida.

**Study supervision:** Lautenschlager, Cox, Flicker.

**Financial Disclosures:** None reported.

**Funding/Support:** This study was supported by grant 303172 from the National Health and Medical Research Council of Australia (Drs Lautenschlager, Almeida, Flicker, Cox and Foster).

**Role of the Sponsors:** The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

**Additional Contributions:** We thank FABS participants and research staff.

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