

Exercise Is Associated with Reduced Risk for Incident Dementia among Persons 65 Years of Age and Older

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Background: Alzheimer disease and other dementing disorders are major sources of morbidity and mortality in aging societies. Proven strategies to delay onset or reduce risk for dementing disorders would be greatly beneficial.

Objective: To determine whether regular exercise is associated with a reduced risk for dementia and Alzheimer disease.

Design: Prospective cohort study.

Setting: Group Health Cooperative, Seattle, Washington.

Participants: 1740 persons older than age 65 years without cognitive impairment who scored above the 25th percentile on the Cognitive Ability Screening Instrument (CASI) in the Adult Changes in Thought study and who were followed biennially to identify incident dementia.

Measurements: Baseline measurements, including exercise frequency, cognitive function, physical function, depression, health conditions, lifestyle characteristics, and other potential risk factors for dementia (for example, apolipoprotein E ϵ 4); biennial assessment for dementia.

Results: During a mean follow-up of 6.2 years (SD, 2.0), 158 participants developed dementia (107 developed Alzheimer disease). The incidence rate of dementia was 13.0 per 1000 person-years for participants who exercised 3 or more times per week compared with 19.7 per 1000 person-years for those who exercised fewer than 3 times per week. The age- and sex-adjusted hazard ratio of dementia was 0.62 (95% CI, 0.44 to 0.86; $P = 0.004$). The interaction between exercise and performance-based physical function was statistically significant ($P = 0.013$). The risk reduction associated with exercise was greater in those with lower performance levels. Similar results were observed in analyses restricted to participants with incident Alzheimer disease.

Limitations: Exercise was measured by self-reported frequency. The study population had a relatively high proportion of regular exercisers at baseline.

Conclusion: These results suggest that regular exercise is associated with a delay in onset of dementia and Alzheimer disease, further supporting its value for elderly persons.

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Alzheimer disease and other dementing illnesses are major sources of morbidity and mortality (1–3) that affect millions of persons in the increasingly aging society of the United States. Research designed to discover strategies to delay onset and progression of these potentially devastating illnesses is ongoing worldwide. Effective prevention strategies would result in substantial benefits through improved quality of life, prolonged independent life expectancy, and reduced economic cost and social burdens. Regular physical exercise is an important element in overall health promotion (4) and might also be an effective strategy to delay onset of dementia (5). A biological basis for how physical exercise might preserve brain function includes improved cerebral blood flow and oxygen delivery (6) and inducing fibroblast growth factor in the hippocampus (7). More recent evidence suggests that reduced loss of hippocampal brain tissue in the aging brain is related to level of physical fitness (8). Evidence from some longitudinal studies and randomized trials suggests that physical exercise enhances cognitive function in older adults (9–15), whereas other studies have failed to observe the benefits of physical exercise in preserving cognitive function (16–19).

Many people regard Alzheimer disease as one of the most dreaded consequences of aging. If regular physical exercise were shown to be effective in reducing the risk or delaying the onset of dementing illnesses, it would be another compelling reason to promote physical exercise. Few population-based longitudinal studies have examined the

role of physical exercise on the risk for dementia in elderly persons. One recent longitudinal study showed that physical exercise was associated with decreased risk for decline in cognitive function (odds ratio [OR], 0.58), Alzheimer disease (OR, 0.50), and any dementia (OR, 0.63) (11), whereas another longitudinal study showed no association between physical exercise and dementia (16). More recent studies showed that walking was associated with a reduced risk for dementia and Alzheimer disease in a cohort of Japanese-American men (20) and that engaging in more diverse physical activities was associated with a reduced risk for dementia in the Cardiovascular Health Study (21).

The purpose of this study was 2-fold: 1) to determine whether regular exercise is associated with a reduced risk for incidence of dementia (in particular, Alzheimer disease) in a cohort followed biennially over 6 years and 2) to

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Context

Some studies suggest that people with high levels of physical activity are less likely to develop dementia.

Content

All 1740 participants in this cohort study were 65 years of age or older and were cognitively intact at baseline. Over 6.2 years, the rate of dementia was 13.0 per 1000 person-years in those who exercised 3 or more times per week and 19.7 per 1000 person-years in those who exercised less than 3 times per week.

Limitations

The only measure of exercise intensity was self-reported frequency. The cohort was largely white and well-educated.

Implications

This study adds to the evidence that regular exercise is associated with a lower risk for dementia. However, the existing evidence does not prove that regular exercise is associated with a lower dementia risk.

—The Editors

examine whether the association of physical exercise with incident dementia is modulated by other potential risk factors, such as depression, cardiovascular and cerebrovascular disease, diabetes, apolipoprotein E $\epsilon 4$ allele, cognitive function, physical function, self-rated health, and lifestyle characteristics.

METHODS**Study Sample**

The Adult Changes in Thought (ACT) study is a population-based, longitudinal study of aging and dementia. The ACT study was designed to determine the incidence of Alzheimer disease, other types of dementia, and cognitive impairment as well as to determine risk factors for these conditions. The details of the ACT study have been described elsewhere (22, 23). Briefly, a random sample of 6782 individuals was drawn from Seattle-area members of Group Health Cooperative (GHC), a consumer-governed health maintenance organization. The participants were 65 years of age and older when the study began in 1994 to 1996. Those who had an existing diagnosis of dementia, were current residents of a nursing home, or were participating in other studies were ineligible ($n = 1360$). Of 5422 eligible persons, 2581 participated and 2841 declined participation. Age, sex, and ethnicity of the remaining 2581 participants did not differ significantly from those who were excluded. Nonresponse has been described elsewhere (22). Declining to participate was more common among the oldest age group (> 85 years), women, and African-American and minority groups (22). Additional

details regarding the incident rates of dementia and Alzheimer disease from the ACT study have been published elsewhere and are consistent with rates reported in U.S. and European cohort studies (22). The institutional review boards of the University of Washington and Group Health Cooperative approved the ACT study.

Participants received the Cognitive Ability Screening Instrument (CASI) (24) as initial screening for cognitive function and were interviewed with structured questionnaires to obtain data, including demographic characteristics, medical history, memory and general functioning, and potential epidemiologic risk factors. Persons scoring 86 or higher on the CASI were entered directly into the ACT cohort as being cognitively intact. (The CASI scores range from 0 to 100; a score of 86 corresponds to a Mini-Mental State Examination score of 25 to 26.) Persons with a score lower than 86 had additional medical record review and standardized clinical and neuropsychological evaluation for dementia. Persons who did not meet established criteria for dementia (25) were included in the ACT cohort.

The current study sample was selected from the 2581 ACT participants to examine the temporal relationship of physical exercise preceding development of dementia. By design, we selected the 1895 persons whose CASI scores were above the 25th percentile—CASI scores 91 to 100. We excluded 686 persons whose CASI scores were in the lowest quartile—CASI scores 62 to 90—because the lowest quartile group might include persons who had mild cognitive impairment or impending dementia (26). We did not collect information about the history of exercise before the participants entered the study. Therefore, in the group with low CASI scores, we could not be certain whether a reported low level of physical exercise preceded the development of dementia or was a consequence of the development of cognitive impairment or dementia. Of 1895 participants selected, 155 withdrew after the baseline visit and did not have a follow-up examination and were thus excluded from the analyses, leaving the analytic sample of 1740 persons.

Incident Dementia

We conducted biennial examinations to identify cases of incident dementia, when participants were rescreened with the CASI. Those who scored 86 or higher on the CASI remained in the ACT cohort. Scores on the CASI that were less than 86 at follow-up prompted a full standardized clinical examination. The results of rescreening by the CASI and by the clinical and neuropsychological examinations were reviewed at a consensus diagnosis conference that included at least the examining physician, a neuropsychologist, another study physician, and the study nurse. Persons who did not meet the criteria for dementia were considered as not having dementia and were followed in the ACT cohort (22, 23). Persons who met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), criteria (25) for dementia were consid-

ered to have incident dementia. Dementia type was determined by the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria (27) for Alzheimer disease and by the DSM-IV criteria (25) for other types of dementia. Level of physical activity was not considered at the consensus conference.

Physical Exercise

Physical exercise was assessed at baseline by asking participants the number of days per week they did each of the following activities for at least 15 minutes at a time during the past year: walking, hiking, bicycling, aerobics or calisthenics, swimming, water aerobics, weight training or stretching, or other exercise. The frequency of exercise was calculated by the times per week that participants engaged in any of these forms of exercise. In this study, persons who exercised at least 3 times a week, above the lowest quartile, were classified as exercising regularly.

Baseline Variables as Potential Confounders

Numerous factors may influence the relationship between exercise and risk for dementia, including physical functioning, cognitive function, depression, health conditions, and lifestyle characteristics. Physical function was assessed by a performance-based physical function (PPF) test (23), which consisted of 4 performance tests: 10-foot timed walk, time to stand from a seated position in a chair to a standing position 5 times, balance test, and grip strength in the dominant hand. Each test was scored from 0 to 4 points. The final PPF score was the sum of the scores for the 4 performance tests and ranged from 0 to 16; higher scores indicated better physical function. Details of the PPF test have been reported elsewhere (23).

Cognitive function was assessed by using the CASI, which provides quantitative assessment of attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, list-generating fluency, abstraction, and judgment (24). At baseline, depression was measured by using the 11-item Center for Epidemiologic Studies Depression (CES-D) scale (28). The CES-D scores ranged from 0 to 33, with higher scores representing more depressive symptoms.

Health conditions were assessed by self-rated health and self-reported medical conditions. Participants were asked to rate their health as excellent, very good, good, fair or poor. They were also asked whether a doctor had ever told them that they had diabetes mellitus or high blood sugar, hypertension, congestive heart failure, heart attack, angina pectoris, stroke, cerebral hemorrhage, or small strokes or transient ischemic attacks or whether they had ever had coronary bypass surgery. Coronary heart disease included congestive heart failure, heart attack, angina pectoris, and coronary artery bypass surgery. Cerebrovascular disease included stroke, cerebral hemorrhage, and small strokes or transient ischemic attacks.

The lifestyle characteristics assessed included smoking,

consuming alcohol, and taking dietary supplements. Participants were asked at baseline whether they had smoked 100 cigarettes in their lifetime and whether they smoked currently; they were then classified as nonsmokers, former smokers, or current smokers. To assess alcohol consumption, participants were asked at baseline whether they had more than 5 drinks in the past year and whether they had problems because of drinking. Nondrinkers were those who had fewer than 5 drinks a year; drinkers were those who had 5 drinks or more a year but did not have any problems related to alcohol consumption; and problem drinkers were those who reported problems related to alcohol consumption. Participants were also asked whether they had taken vitamins or dietary supplements, including vitamin A, vitamin C, vitamin E, multivitamins, and fish oil supplements, for at least 1 week in the previous month. Demographic variables of age, sex, ethnicity, and years of education were included. Apolipoprotein E genotype, a genetic risk factor for Alzheimer disease (29, 30), was also included.

Statistical Analysis

To investigate which baseline factors were associated with physical exercise, age- and sex-adjusted odds ratios of exercising regularly (≥ 3 times/week) were obtained by using logistic regression. Exercise was the response variable, and each of the other baseline variables was fitted into a separate model adjusting for age and sex.

To evaluate the temporal relationship of exercise with incident dementia, we used Cox proportional hazards regression models (31). Because dementia is highly age-related, we used years of age during the study as the time axis, with left truncation at age of entering the study, and kept age at baseline as a covariate in Cox models. Thereby, age was completely adjusted for in our analyses. The primary outcome was age of onset of dementia. The risk factor of primary interest was exercise at baseline. Persons who left the study before developing dementia were censored at their last examinations. Persons who remained dementia-free during the study were censored at the most recent follow-up date. The Schoenfeld residual test (32) was used to check the proportional hazards assumption. The age- and sex-adjusted hazard ratio of dementia by exercise was estimated from the Cox model.

To investigate which baseline factors influence the association of exercise with incident dementia, we fit a separate Cox model on potentially confounding baseline variables by keeping exercise as the primary predictor and adjusting for age and sex. We examined whether the hazard ratio of dementia for exercise was changed by adding the baseline variable into a model. To further examine potential effect modifications, the interaction terms of exercise and each baseline variable were added into those Cox models. Effect modification was considered to be present if the coefficient for the interaction was found to be statistically significant ($P < 0.05$). Finally, we examined the hazard

ratio of dementia for exercise by adjusting for all potential confounders simultaneously. For the principal analyses reported here, we compared participants in the lowest quartile of frequency of exercise (< 3 times/week) with those in the top 3 quartiles. As a secondary analysis to determine whether there was a dose-response relationship of exercise, we compared participants in each quartile group of exercise frequency by assessing hazard ratios for the second, third, and fourth quartiles, compared with the lowest quartile (< 3 times/week).

Sensitivity analyses were conducted to evaluate whether a potential bias could be introduced by the censoring mechanism for persons who withdrew from the study or died. Because persons who had poor cognitive function (that is, a low CASI score) when they left the study would be more likely to develop dementia, the random censoring assumption for those persons might not be appropriate. We examined the last CASI scores for persons

who withdrew or died. If a person's last CASI score was less than 86 before he or she left the study, we assumed that the person would develop dementia 1 year after the last visit. We then repeated the analyses to determine whether the association of exercise and incident dementia was changed. Statistical analyses were conducted by using Stata software, version 7 (Stata Corp., College Station, Texas).

Role of the Funding Source

The funding source did not play a role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Study participants were followed from May 1994 to October 2003, with a mean follow-up of 6.2 years (SD, 2.0). Of 1740 participants, 1185 remained dementia-free,

Table 1. Baseline Characteristics by Follow-up Status*

Variable	Participants Free of Dementia (n = 1185)	Participants with Dementia (n = 158)	Participants Who Died or Withdrew (n = 397)	P Value†
Participants who exercised at least 3 times per week, n (%)	915 (77.2)	106 (67.1)	274 (69.0)	<0.001
Mean age at baseline (SD), y	73.2 (5.1)	78.2 (5.5)	76.3 (6.4)	<0.001, <0.001
Female sex, n (%)	731 (61.9)	93 (58.9)	223 (56.2)	0.117
Race, n (%)				
White	1109 (93.7)	154 (97.5)	371 (93.4)	
Black	20 (1.7)	1 (0.6)	8 (2.0)	
Other races	55 (4.6)	3 (1.9)	18 (4.5)	0.410
Supplement use, n (%)				
Vitamin A	165 (13.9)	14 (8.9)	51 (12.8)	0.204
Vitamin C	482 (40.7)	50 (31.6)	154 (38.8)	0.089
Vitamin E	389 (32.8)	48 (30.4)	122 (30.7)	0.656
Multivitamin	566 (47.8)	80 (50.6)	192 (48.4)	0.791
Fish oil	52 (4.4)	10 (6.3)	21 (5.3)	0.481
Any supplement	764 (64.5)	101 (63.9)	251 (63.2)	0.903
Smoking status, n (%)				
Nonsmoker	570 (48.1)	69 (43.7)	163 (41.1)	
Former smoker	539 (45.5)	81 (51.3)	201 (50.6)	
Current smoker	76 (6.4)	8 (5.1)	33 (8.3)	0.091
Alcohol use, n (%)				
Nondrinker	498 (42.0)	79 (50.0)	196 (49.4)	
Drinker	590 (49.8)	68 (43.0)	164 (41.3)	
Problem drinker	97 (8.2)	11 (7.0)	37 (9.3)	0.028
Comorbid conditions, n (%)				
Coronary heart disease	179 (15.1)	39 (24.8)	103 (25.9)	<0.001
Cerebrovascular disease	72 (6.1)	22 (13.9)	45 (11.4)	<0.001
Hypertension	404 (34.2)	74 (47.1)	181 (45.8)	<0.001
Diabetes	97 (8.2)	16 (10.1)	45 (11.3)	0.149
Self-rated health status, n (%)				
Excellent	166 (14.0)	5 (3.2)	28 (7.0)	
Very good	449 (37.9)	50 (31.6)	89 (22.4)	
Good	459 (38.7)	77 (48.7)	176 (44.3)	
Fair	106 (9.0)	21 (13.3)	92 (23.2)	
Poor	5 (0.4)	5 (3.2)	12 (3.0)	<0.001
Mean education (SD), y	14.4 (2.7)	14.2 (2.7)	14.0 (2.9)	0.380, 0.011
Mean Cognitive Ability Screening Instrument score at baseline (SD)	95.5 (2.4)	94.2 (2.3)	94.7 (2.3)	<0.001, <0.001
Mean Center for Epidemiologic Studies Depression Scale score at baseline (SD)	3.6 (3.7)	5.1 (4.7)	4.6 (4.6)	<0.001, <0.001
Mean physical performance functioning score at baseline (SD)	13.0 (2.3)	11.5 (3.0)	11.6 (3.2)	<0.001, <0.001
Participants with any ApoE ε4 alleles, n (%)	251 (21.2)	52 (32.9)	87 (21.9)	0.004

* ApoE = apolipoprotein E.

† Cells with 2 P values indicate the P values for the t-tests comparing means of those who remained dementia-free with those who developed dementia, and means of those who remained dementia-free with those who withdrew or died.

Table 2. Baseline Characteristics of Study Participants by Exercise Levels*

Variable	Participants Who Exercised Fewer than 3 Times per Week (n = 445)	Participants Who Exercised 3 or More Times per Week (n = 1295)	P Value
Mean age at baseline (SD), y	74.5 (5.8)	74.3 (5.7)	0.633
Female sex, n (%)	278 (62.5)	772 (59.6)	0.288
Race, n (%)			
White	418 (93.9)	1216 (94.0)	
Black	11 (2.5)	18 (1.4)	
Other races	16 (3.6)	60 (4.6)	0.208
Supplement use, n (%)			
Vitamin A	61 (13.7)	169 (13.0)	0.724
Vitamin C	157 (35.3)	529 (40.8)	0.038
Vitamin E	128 (28.8)	431 (33.3)	0.078
Multivitamin	194 (43.6)	644 (49.7)	0.025
Fish oil	25 (5.6)	58 (4.5)	0.331
Any supplement	264 (59.3)	852 (65.8)	0.014
Smoking status, n (%)			
Nonsmoker	193 (43.4)	609 (47.0)	
Former smoker	214 (48.1)	607 (46.9)	
Current smoker	38 (8.5)	79 (6.1)	0.136
Alcohol use, n (%)			
Nondrinker	213 (47.9)	560 (43.2)	
Drinker	189 (42.5)	633 (48.9)	
Problem drinker	43 (9.7)	102 (7.9)	0.057
Comorbid conditions, n (%)			
Coronary heart disease	79 (17.8)	242 (18.7)	0.661
Cerebrovascular disease	43 (9.7)	96 (7.4)	0.131
Hypertension	170 (38.3)	489 (37.9)	0.886
Diabetes	36 (8.1)	122 (9.4)	0.399
Self-rated health status, n (%)			
Excellent	37 (8.3)	162 (12.5)	
Very good	130 (29.2)	458 (35.4)	
Good	193 (43.4)	519 (40.1)	
Fair	70 (15.7)	149 (11.5)	
Poor	15 (3.4)	7 (0.5)	<0.001
Mean education (SD), y	13.9 (2.6)	14.4 (2.8)	0.001
Mean Cognitive Ability Screening Instrument score at baseline (SD)	95.1 (2.4)	95.3 (2.4)	0.343
Mean Center for Epidemiologic Studies Depression score at baseline (SD)	4.6 (4.3)	3.8 (4.0)	<0.001
Mean Physical Performance Functioning score at baseline (SD)	12.0 (3.0)	12.8 (2.5)	<0.001
Participants with any ApoE ε4 alleles, n (%)	100 (22.5)	290 (22.4)	0.973

* ApoE = apolipoprotein E.

158 developed dementia (107 developed Alzheimer disease, 33 developed vascular dementia, and 18 developed other types of dementia), 121 withdrew, and 276 died. **Table 1** shows the baseline characteristics of study participants who remained dementia-free, developed dementia, withdrew from the study, or died. **Table 2** shows the baseline characteristics of study participants by levels of exercise.

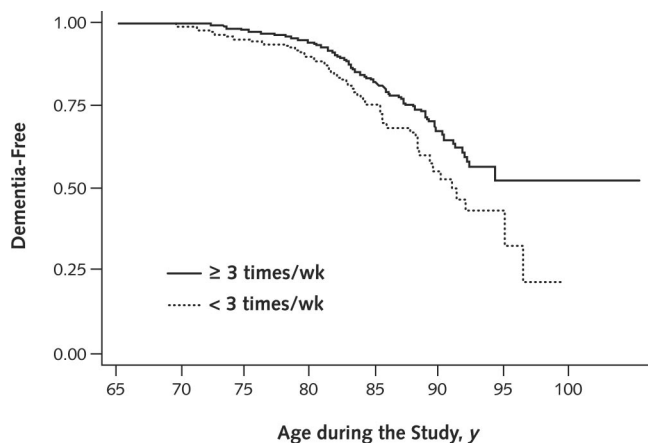
Baseline variables associated with exercise were self-rated health, PPF scores, CES-D scores, smoking, dietary supplements, and years of education. Odds ratios of doing regular exercise were 0.62 (95% CI, 0.41 to 0.92; $P = 0.016$), 0.49 (CI, 0.31 to 0.77; $P = 0.002$), and 0.10 (CI, 0.04 to 0.27; $P < 0.001$) for participants who rated their health as good, fair, and poor, respectively, compared with those who rated their health as excellent. In addition, ORs were 1.13 (CI, 1.08 to 1.17; $P < 0.001$) per 1-point in-

crement of PPF scores; 0.96 (CI, 0.93 to 0.98; $P = 0.001$) per 1-point increment of CES-D scores; 0.64 (CI, 0.42 to 0.98; $P = 0.039$) for current smokers compared with nonsmokers; 1.35 (CI, 1.08 to 1.69; $P = 0.009$) for persons who took dietary supplements; and 1.07 (CI, 1.02 to 1.11; $P = 0.002$) for 1-year increment of education.

The incidence rate of dementia was 13.0 per 1000 person-years for persons who exercised 3 or more times per week, compared with 19.7 per 1000 person-years for persons who exercised fewer than 3 times per week. In **Figure 1**, Kaplan–Meier survival estimates show that participants who exercised 3 or more times per week had a higher probability of being dementia-free than those who exercised fewer than 3 times per week. The age- and sex-adjusted hazard ratio of dementia for the regular exercise group was 0.62 (CI, 0.44 to 0.86; $P = 0.004$).

The point estimate and confidence interval of the haz-

Figure 1. Kaplan–Meier survival estimates for the probabilities of being dementia-free.



Persons who exercised 3 or more times per week were more likely to be dementia-free than those who exercised fewer than 3 times per week.

ard ratio of dementia for exercise changed negligibly each time we added a single covariate to the model. Covariates that were considered included alcohol consumption, smoking, supplement use, education, presence of apolipoprotein E $\epsilon 4$ alleles, diabetes, hypertension, cerebrovascular disease, coronary heart disease, self-rated health, physical performance, depression, and cognitive functioning. We found that alcohol consumption, smoking, supplement use, and level of education were not associated with dementia and that adjusting for those variables did not change the point estimate for exercise; therefore, they were not included as potential confounders in the final model. When potential confounders were simultaneously adjusted for, the hazard ratio of dementia by exercise was 0.68 (CI, 0.48 to 0.96; $P = 0.030$).

The interaction of exercise and PPF scores was statistically significant ($P = 0.013$). In **Figure 2**, Kaplan–Meier estimates show probabilities of being dementia-free by exercise at different PPF levels. The risk reduction of dementia by exercise was greater among participants with lower PPF scores than among those with higher PPF scores. The adjusted hazard ratios of dementia by exercise were 0.58 (CI, 0.39 to 0.84; $P = 0.004$), 0.66 (CI, 0.46 to 0.94; $P = 0.023$), and 0.75 (CI, 0.51 to 1.09; $P = 0.126$) for persons with PPF scores of 10, 11, and 12, respectively. Among those who exercised fewer than 3 times per week, a 1-point increment of PPF score was associated with a hazard ratio of dementia of 0.89 (CI, 0.82 to 0.96; $P = 0.004$), whereas among those who exercised 3 or more times per week, each additional 1-point increment of PPF score was associated with a hazard ratio of dementia of 1.01 (CI, 0.93 to 1.09; $P = 0.762$).

To examine the association of exercise with incidence of Alzheimer disease, we kept Alzheimer disease ($n = 107$)

as incident cases and recoded other types of dementia ($n = 51$) as being censored at the time of diagnosis. The age- and sex-adjusted hazard ratio of Alzheimer disease by exercise was 0.64 (CI, 0.43 to 0.96; $P = 0.031$). After we adjusted for potential confounders, the hazard ratio of Alzheimer disease by exercise was 0.69 (CI, 0.45 to 1.05; $P = 0.081$). The interaction of exercise with PPF scores was also found in relation to Alzheimer disease ($P = 0.021$).

When persons who withdrew from the study or died were compared with those who were followed and remained dementia-free, persons who withdrew were older and less likely to exercise regularly; had lower CASI scores, lower PPF scores, and higher CES-D scores; were more likely to have medical conditions, such as coronary heart disease, cardiovascular disease, and hypertension; and were more likely to report their health as poor, fair, or good at baseline. The mean final CASI score for persons who withdrew or died was 92.8, compared with 94.2 for persons who remained in the study. Of 397 participants who withdrew or died, 39 had a final CASI score of less than 86. Of these 39 participants, 12 (31%) exercised fewer than 3 times per week at baseline. These participants who had a CASI score of less than 86 were recoded as having incident dementia 1 year after leaving the study. We then repeated the analyses and found that the age- and sex-adjusted hazard ratio of dementia by exercise was 0.63 (CI, 0.46 to 0.84; $P = 0.002$.) After adjustment for potential confounders, the hazard ratio of dementia by exercise was 0.70 (CI, 0.51 to 0.96; $P = 0.026$). The interaction of exercise and PPF scores in relation to dementia also was not changed.

DISCUSSION

This population-based, longitudinal study involving the ACT cohort found a reduced incidence rate of dementia for persons who exercised 3 or more times a week (13.0 per 1000 person-years) compared with those who exercised fewer than 3 times per week (19.7 per 1000 person-years). Persons who exercised 3 or more times a week had a relative hazard of 0.68 (CI, 0.48 to 0.96) for developing dementia compared with those who exercised fewer than 3 times per week when potential confounders were adjusted for; this corresponds to a 32% reduction in risk for dementia. Exercise seemed to be associated with the greatest risk reduction in participants who had poor physical functioning at baseline.

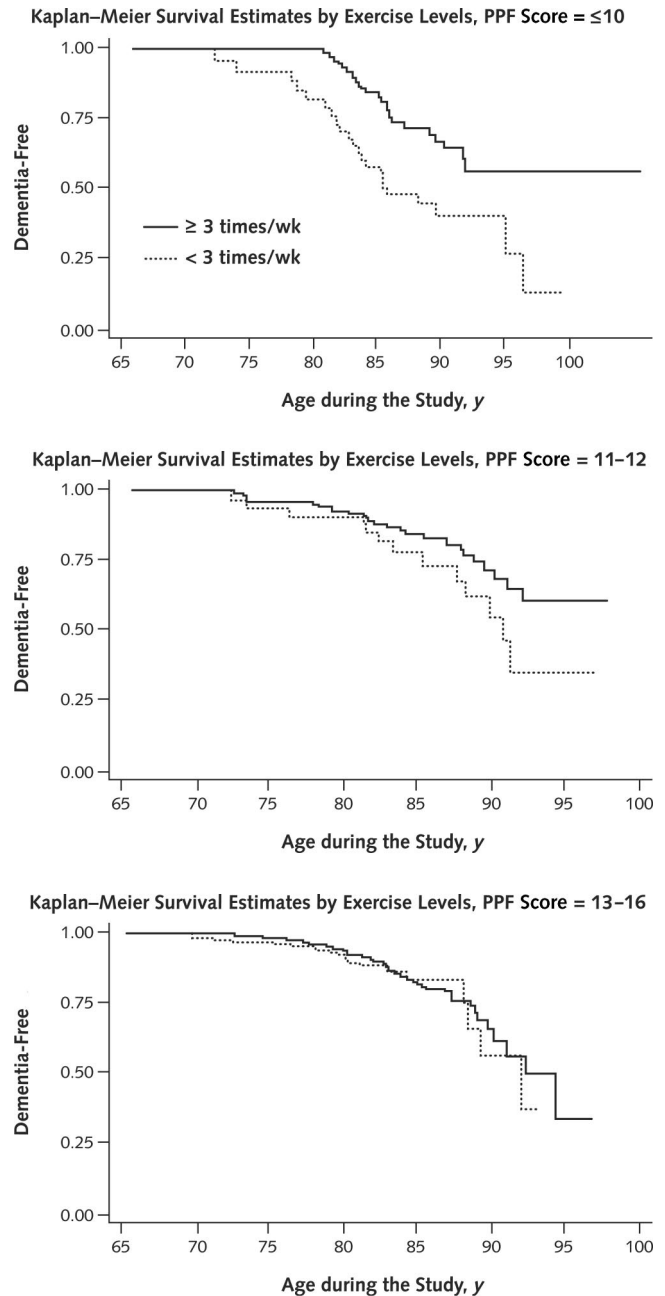
Some longitudinal studies of the relationship between physical exercise and dementia, Alzheimer disease, and cognitive decline have observed a protective association, whereas others have failed to find this association. One unique feature of our study is the effort we made in our design to reduce the potential effect that changes in physical exercise related to the so-called prodromal phase of dementia might have on our results. It is now widely accepted that manifestations of behavior changes (including

decline in habitual exercise) related to Alzheimer disease and other types of dementia with insidious onset can occur years before a person crosses a threshold that allows a definitive diagnosis of dementia to be made (33, 34). Although enrollment in the ACT cohort was restricted to persons without dementia, we deliberately set a higher threshold for eligibility in our study, eliminating persons with CASI scores in the lowest quartile and thereby reducing the potential for this classification error.

In our study, the magnitude of the reduced risk was similar regardless of the adjustments we considered. Our study only measured frequency of exercise, and we used it only to distinguish more regular exercisers from nonexercisers. We did not have a good measure of intensity and duration for calculating the dose of exercise and, not surprisingly, did not find a dose–response effect for exercise frequency divided into quartiles. Compared with persons who were in the lowest quartile (exercised < 3 times/week), persons who were in the second quartile (exercised 3 to 5 times/week) had a relative hazard of dementia of 0.57 (CI, 0.36 to 0.87; $P = 0.009$), those in the third quartile (exercised 6 to 7 times/week) had a relative hazard of 0.55 (CI, 0.35 to 0.88; $P = 0.012$), and those in the highest quartile (exercised > 7 times/week) had a relative hazard of 0.72 (CI, 0.48 to 1.06; $P = 0.111$). It is interesting that investigators from the Centers for Disease Control and Prevention, using Behavioral Risk Factor Surveillance System data, did not find a linear dose–response relationship between exercise duration and intensity and health-related quality of life. Instead, they found a more curvilinear relationship, with better health-related quality of life associated with moderate levels of exercise compared with no exercise or longer duration and higher frequency of exercise (35). Additional research should evaluate the threshold of exercise for a biological benefit related to increased oxygen delivery (6), improved circulation, induced fibroblast growth in the hippocampus (7), and reduced cell loss in sensitive areas like the hippocampus (8) in a general population of free-living elderly persons. The threshold may be quite low, especially in persons at lower levels of physical performance. Our measure of exercise also did not include information about work and nonleisure activities or changes after baseline, and our adjustments in potential confounders are probably incomplete. Thus, residual confounding might explain some of the association we observed. We also acknowledge that our population is relatively homogeneous and contained a relatively high proportion of persons who engaged in physical exercise.

Our study found a potentially important effect modification between exercise and physical functioning in relation to incident dementia as well as Alzheimer disease. There was a greater risk reduction of dementia by exercise among persons with lower levels of physical functioning compared with those with higher levels of physical functioning. Low levels of physical functioning were associated with an increased risk for dementia among persons who

Figure 2. Kaplan–Meier survival estimates by exercise and performance-based physical function (PPF) levels.



Persons who exercised 3 or more times per week had a higher probability of being dementia-free than those who exercised fewer than 3 times per week if their PPF score was less than 13. This relative risk reduction of dementia by exercise was greater among persons with lower PPF scores than among those with higher PPF scores.

exercised fewer than 3 times per week; however, this increased risk diminished among persons who exercised 3 or more times per week. Our finding suggests that one of the ways that exercise might reduce the risk for dementia is through modulating the relationship between physical

functioning and dementia—an area worthy of additional investigation. The shape of the survival curves in **Figures 1 and 2** suggests that exercise does not prevent dementia but might be associated with a delay in onset. If these post hoc findings are confirmed, senior citizens may have more reason to “use it even after you are losing it.”

Our results are consistent with earlier observations that modest levels of physical exercise are associated with delayed onset of dementia or Alzheimer disease (11, 20, 36). We believe that these findings are supported by experimental studies in healthy elderly persons, which showed that a conditioning program improves higher-order cognitive functions (typically executive function, memory, or visuospatial function [37–40]). Changes in such higher-order functions are typically the first signs and symptoms of Alzheimer disease, the most common dementing illness. Our results might be explained by the recent interesting finding that the area of the brain most susceptible to ischemic damage (the hippocampus), which is also one of the earliest areas of the brain to be affected by Alzheimer disease, had less tissue loss in older persons at higher levels of physical conditioning (8).

We believe these findings may be useful if they are confirmed because Alzheimer disease is one of the most feared illnesses of aging and is frequently cited as a reason for not wanting to “get old”: People do not want to lose their independence and quality of life as a consequence of aging (41). Physicians and health-promotion programs might find this information valuable as our society works to find truly effective ways to promote physical activity for all its well-known benefits (42). Indeed, a recent randomized trial demonstrated that increasing the level of physical activity through habitual exercise also benefits persons with established Alzheimer disease (43, 44). Future research is needed to investigate the issue of the dose-versus-threshold-based association between exercise and onset of dementia and the relationship among physical function, exercise, and the onset of dementia.

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References

- Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L, et al. Survival after initial diagnosis of Alzheimer disease. *Ann Intern Med.* 2004;140:501-9. [PMID: 15068977]
- Ganguli M, Rodriguez EG. Reporting of dementia on death certificates: a community study. *J Am Geriatr Soc.* 1999;47:842-9. [PMID: 10404929]
- Ewbank DC. Deaths attributable to Alzheimer's disease in the United States. *Am J Public Health.* 1999;89:90-2. [PMID: 9987474]
- Larson EB, Wang L. Exercise, aging, and Alzheimer disease [Editorial]. *Alzheimer Dis Assoc Disord.* 2004;18:54-6. [PMID: 15249847]
- Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA.* 1995;273:402-7. [PMID: 7823386]
- Rogers RL, Meyer JS, Mortel KF. After reaching retirement age physical activity sustains cerebral perfusion and cognition. *J Am Geriatr Soc.* 1990;38:123-8. [PMID: 2299115]
- Gómez-Pinilla F, So V, Kesslak JP. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. *Neuroscience.* 1998;85:53-61. [PMID: 9607702]
- Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci.* 2003;58:176-80. [PMID: 12586857]
- Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. Ageing, fitness and neurocognitive function [Letter]. *Nature.* 1999;400:418-9. [PMID: 10440369]
- Barnes DE, Yaffe K, Satariano WA, Tager IB. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *J Am Geriatr Soc.* 2003;51:459-65. [PMID: 12657064]
- Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol.* 2001;58:498-504. [PMID: 11255456]
- Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med.* 2001;161:1703-8. [PMID: 11485502]
- Williams P, Lord SR. Effects of group exercise on cognitive functioning and mood in older women. *Aust N Z J Public Health.* 1997;21:45-52. [PMID: 9141729]
- Okumiya K, Matsubayashi K, Wada T, Kimura S, Doi Y, Ozawa T. Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age. *J Am Geriatr Soc.* 1996;44:569-72. [PMID: 8617907]
- Moul JL, Goldman B, Warren B. Physical activity and cognitive performance in the older population. *J Aging Phys Act.* 1995;3:135-45.
- Broe GA, Creasey H, Jorm AF, Bennett HP, Casey B, Waite LM, et al. Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption. *Aust N Z J Public Health.* 1998;22:621-3. [PMID: 9744220]
- Hill RD, Storandt M, Malley M. The impact of long-term exercise training on psychological function in older adults. *J Gerontol.* 1993;48:P12-7. [PMID: 8418145]
- Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med.* 2003;348:2508-16. [PMID: 12815136]
- Madden DJ, Blumenthal JA, Allen PA, Emery CF. Improving aerobic capacity in healthy older adults does not necessarily lead to improved cognitive performance. *Psychol Aging.* 1989;4:307-20. [PMID: 2803624]
- Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. *JAMA.* 2004;292:1447-53. [PMID: 15383515]
- Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, et al. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *Am J Epidemiol.* 2005;161:639-51. [PMID: 15781953]
- Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol.* 2002;59:1737-46. [PMID: 12433261]
- Wang L, van Belle G, Kukull WB, Larson EB. Predictors of functional change: a longitudinal study of nondemented people aged 65 and older. *J Am*

- Geriatr Soc. 2002;50:1525-34. [PMID: 12383150]
24. **Teng EL, Hasegawa K, Homma A, Imai Y, Larson E, Graves A, et al.** The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. *Int Psychogeriatr.* 1994;6:45-58; discussion 62. [PMID: 8054493]
25. **American Psychiatric Association.** Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
26. **Wang L, van Belle G, Crane PK, Kukull WA, Bowen JD, McCormick WC, et al.** Subjective memory deterioration and future dementia in people aged 65 and older. *J Am Geriatr Soc.* 2004;52:2045-51. [PMID: 15571540]
27. **McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM.** Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-44. [PMID: 6610841]
28. **Radloff LS.** The CES-D scale: a self-reported depression scale for research in general population. *Appl Psychol Meas.* 1977;1:385-401.
29. **Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, et al.** Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A.* 1993;90:1977-81. [PMID: 8446617]
30. **Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, et al.** Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. *N Engl J Med.* 1995;333:1242-7. [PMID: 7566000]
31. **Cox DR.** Regression models in life tables (with discussion). *J R Stat Soc [Ser B].* 1972;34:187-220.
32. **Grambsch PM, Therneau TM.** Proportional hazard tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81:515-26.
33. **Linn RT, Wolf PA, Bachman DL, Knoefel JE, Cobb JL, Belanger AJ, et al.** The "preclinical phase" of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. *Arch Neurol.* 1995;52:485-90. [PMID: 7733843]
34. **McCormick WC, Kukull WA, van Belle G, Bowen JD, Teri L, Larson EB.** Symptom patterns and comorbidity in the early stages of Alzheimer's disease. *J Am Geriatr Soc.* 1994;42:517-21. [PMID: 8176147]
35. **Brown DW, Brown DR, Heath GW, Balluz L, Giles WH, Ford ES, et al.** Associations between physical activity dose and health-related quality of life. *Med Sci Sports Exerc.* 2004;36:890-6. [PMID: 15126726]
36. **Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F.** Physical activity, including walking, and cognitive function in older women. *JAMA.* 2004;292:1454-61. [PMID: 15383516]
37. **Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al.** Ageing, fitness and neurocognitive function [Letter]. *Nature.* 1999;400:418-9. [PMID: 10440369]
38. **Shay KA, Roth DL.** Association between aerobic fitness and visuospatial performance in healthy older adults. *Psychol Aging.* 1992;7:15-24. [PMID: 1558699]
39. **Hawkins HL, Kramer AF, Capaldi D.** Aging, exercise, and attention. *Psychol Aging.* 1992;7:643-53. [PMID: 1466833]
40. **Dustman RE, Ruhling RO, Russell EM, Shearer DE, Bonekat HW, Shigeoka JW, et al.** Aerobic exercise training and improved neuropsychological function of older individuals. *Neurobiol Aging.* 1984;5:35-42. [PMID: 6738784]
41. **Phelan EA, Anderson LA, LaCroix AZ, Larson EB.** Older adults' views of "successful aging." *J Am Geriatr Soc.* 2004;54:1559-611. [PMID: 14728629]
42. **U.S. Preventive Services Task Force.** Behavioral counseling in primary care to promote physical activity: recommendation and rationale. *Ann Intern Med.* 2002;137:205-207. [PMID: 12160370]
43. **Teri L, McCurry SM, Buchner DM, Logsdon RG, LaCroix AZ, Kukull WA, et al.** Exercise and activity level in Alzheimer's disease: a potential treatment focus. *J Rehabil Res Dev.* 1998;35:411-9. [PMID: 10220219]
44. **Teri L, Gibbons LE, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, et al.** Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. *JAMA.* 2003;290:2015-22. [PMID: 14559955]

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