A Prospective Study of Physical Activity and Cognitive Decline in Elderly Women

Women Who Walk

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Background: Several studies have suggested that physical activity is positively associated with cognitive function in elderly persons. Evidence about this association has been limited by the cross-sectional design of most studies and by the frequent lack of adjustment for potential confounding variables. We determined whether physical activity is associated with cognitive decline in a prospective study of older women.

Methods: We studied 5925 predominantly white community-dwelling women (aged ≥65 years) who were recruited at 4 clinical centers and were without baseline cognitive impairment or physical limitations. We measured cognitive performance using a modified Mini-Mental State Examination at baseline and 6 to 8 years later. Physical activity was measured by self-reported blocks (1 block ≈ 160 m) walked per week and by total kilocalories (energy) expended per week in recreation, blocks walked, and stairs climbed. Cognitive decline was defined as a 3-point decline or greater on repeated modified Mini-Mental State Examination.

Results: Women with a greater physical activity level at baseline were less likely to experience cognitive decline during the 6 to 8 years of follow-up: cognitive decline occurred in 17%, 18%, 22%, and 24% of those in the highest, third, second, and lowest quartile of blocks walked per week ($P<.001$ for trend). Almost identical results were obtained by quartile of total kilocalories expended per week. After adjustment for age, educational level, comorbid conditions, smoking status, estrogen use, and functional limitation, women in the highest quartile remained less likely than women in the lowest quartile to develop cognitive decline (for blocks walked: odds ratio, 0.66 [95% confidence interval, 0.54-0.82]; for total kilocalories: odds ratio, 0.74 [95% confidence interval, 0.60-0.90]).

Conclusions: Women with higher levels of baseline physical activity were less likely to develop cognitive decline. This association was not explained by differences in baseline function or health status. This finding supports the hypothesis that physical activity prevents cognitive decline in older community-dwelling women.

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AT LEAST 10% of persons older than 65 years and 50% of those older than 85 years have some form of cognitive impairment, ranging from mild deficits to dementia.[1] The identification of risk factors associated with cognitive decline, especially ones that may lead to prevention or intervention strategies, is critical. Physical activity has been identified as a possible risk factor that might be amenable to such interventions. There are several possible mechanisms by which physical activity could affect cognitive function, including increasing cerebral blood flow,[2] reducing the risk of cardiovascular and cerebrovascular disease,[3] and stimulating neuronal growth and survival.[4]

While some studies support the hypothesis that increased levels of physical activity are associated with preserved cognitive function, several methodological considerations limit the ability to draw conclusions from these studies. For example, several cross-sectional studies[5-9] have demonstrated that physically active elderly persons perform better on cognitive testing than inactive elderly persons. However, cause-effect associations are difficult to determine in these cross-sectional studies since it is not clear whether cognitive impairment leads to lower levels of physical activity or vice versa. Only 2 prospective studies have been conducted; one[10] found an association between energy expended from strenuous, but not moderate, activities and preservation of cognitive function over 2 to 3 years in 1011 community-dwelling elderly persons. The subjects in that study were part of a well-functioning group of elderly persons and the measure-

SUBJECTS AND METHODS

SUBJECTS

All women were enrolled in the Study of Osteoporotic Fractures,[12] a prospective study of risk factors for fractures among 9704 predominantly white community-dwelling women 65 years or older. Participants were recruited from population-based listings in 4 areas of the United States: Baltimore, Md; Minneapolis, Minn; the Monongahela Valley near Pittsburgh, Pa; and Portland, Ore. Black women were excluded because of their low incidence of fracture, as were women who were unable to walk without assistance or who had bilateral hip replacements. All participants were interviewed and examined during the baseline visit (1986-1988). Participants then underwent biennial clinic visits and completed annual questionnaires.

Because we were interested in whether physical activity was associated with the risk of developing cognitive decline prospectively, we excluded women with baseline cognitive impairment (modified Mini-Mental State Examination [mMMSE] score <23 of possible 26 [n=950]), women with missing baseline cognitive scores (n=53), women with baseline physical limitations (subjects who said that they were unable to stand up unaided from a chair or to walk up stairs because of an injury or health condition [n=939]), women with missing information on physical limitations (n=10), and women who did not complete baseline physical activity assessments (n=51). Of the remaining 7701 women, 596 (8%) died, 238 (3%) were unavailable for follow-up, and 942 (12%) did not have follow-up cognitive measurements (either 6- or 8-year measurements). The remaining 5925 subjects who completed cognitive tests at baseline and follow-up form the analytic cohort for this study. Women who did not have cognitive follow-up measurements had lower baseline scores on cognitive testing and were less physically active compared with the 5925 women in the final analytical cohort ($P<.001$ for all comparisons). All subjects provided written informed consent, and the study was approved by the committees on human research at each site.

MEASUREMENT OF PHYSICAL ACTIVITY

We measured physical activity at baseline by asking how many city blocks (1 block $\approx$ 160 m) (or the equivalent) the women walked each day for exercise or as part of their normal routine and how many flights of stairs they climbed up each day. We also measured physical activity using a modified Paffenbarger Scale,[13] in which trained interviewers asked the subjects to report the frequency and duration of their participation per week during the past year in 33 different physical activities. Specifically, the women were asked, "Did you participate in any physical activities, recreation, or sport in the past week?" If the answer was yes, the subjects were asked how often (weeks per year and times per week) and for how long they participated in the activity. The activities were classified according to low (walking or gardening), medium (dancing or tennis), or high (jogging or skiing) intensity and assigned energy expenditures of 5.0, 7.5, or 10.0 kcal/min, respectively, according to previously reported methods.[14] Total physical activity, expressed in kilocalories (energy) expended per week, was calculated by adding kilocalories expended in the 33 recreational activities, blocks walked (8 kcal per block), and stairs climbed (4 kcal per flight). For our analyses, our primary measures of physical activity were blocks walked per week and total kilocalories expended per week.

MEASUREMENT OF COGNITIVE FUNCTION

A trained examiner administered the cognitive testing during the baseline clinic visit and at the follow-up visits 6 and 8 years later. The mMMSE, which does not include some

ment of physical activity did not include recreational or walking activities, only daily activities around the house. The other prospective study[11] did not find an association between physical activity and cognitive decline in 327 Australian older men and women followed up for 3 years. However, this study may have had limited power due to a small sample size and a short follow-up.

Therefore, we examined the association between baseline physical activity (daily activities and recreational activities) and cognitive decline during 8 years of follow-up in elderly community-dwelling women participating in an ongoing prospective study. We excluded women with baseline cognitive impairment or physical limitations, and we adjusted for several potential confounders of the association between physical activity and cognitive function, including baseline function and health status.

RESULTS

Women reported a wide range of walking activity, with a median of 49 blocks walked per week. Ten percent of the women never walked for exercise or for daily activities, while 10% walked 200 or more blocks per week. The median numbers (ranges) of blocks walked per week in the lowest, second, third, and highest quartile were 7 (0-22), 28 (23-49), 77 (50-112), and 175 (113-672), respectively. Similarly, the participants reported a wide range of total physical activity, with a median total expenditure of 1323 kcal/wk. Nearly 5% of the women reported that they were completely sedentary, and 5% expended more than 5000 kcal/wk. The median numbers (ranges) expended in the lowest, second, third, and highest quartile were 336 (0-615), 936 (616-1323), 1773 (1324-2414), and 3469 (2415-17531) kcal/wk, respectively. Women in the highest physical activity quartiles (measured by total kilocalories expended) were younger, were more educated, were more likely to be taking estrogen and to drink alcohol, were less likely to smoke, had fewer comorbid medical conditions, had a lower body mass index, had lower depression scores, and had less functional limitation than women in the lower quartiles ($P \leq .05$ for all) (**Table 1**). A similar pattern of differences was seen for women across quartile of blocks walked. Mean±SD mMMSE scores at baseline were slightly, but probably not clinically significantly, lower in the lowest questions assessing orientation, was administered.[15] This is a brief global cognitive function test with concentration, language, and memory components designed to screen for cognitive impairment. The mMMSE has a potential range of 0 to 26, with higher numbers indicating better performance (subjects with baseline scores <23 were excluded from the analytic cohort). We defined cognitive decline as a decrease of 3 or more points on the mMMSE from baseline to the 6- or 8-year follow-up (whichever was lower). This definition has been previously used for the full MMSE to identify the onset of dementia in a group of community-dwelling elderly persons.[16]

OTHER VARIABLES

At the initial study visit, we ascertained age, highest level of education, weekly alcohol use, current smoking, and history of comorbid health conditions (eg, stroke, myocardial infarction, Parkinson disease, diabetes, and hypertension). We asked subjects to rate their overall health compared with other women as excellent, good, fair, poor, or very poor. Functional status was assessed by asking the subjects the amount of difficulty they had with each of 6 activities (preparing meals, shopping, lifting heavy items, dressing, bathing, and transferring) based on a modified version of the Stanford Health Assessment Questionnaire.[17] We defined functional impairment as being present if the respondent reported much difficulty with 1 or more of these activities. The 15-item Geriatric Depression Scale was administered shortly after the study began.[18] Scores range from 0 to 15, with higher scores indicating more symptoms of depression. During each clinic examination, we measured weight and height; body mass index was defined as weight in kilograms divided by the square of height in meters. Participants were asked about current use of oral estrogen therapy, and reports of current medications were checked by examining labels of drugs brought to the clinic. Baseline walking (gait) speed was determined from the average of 2 trials of the time (seconds) needed to walk 12 m.

STATISTICAL ANALYSIS

Because the distributions of blocks walked per week and total kilocalories expended per week were not normally distributed (skewed to the left), we divided subjects into approximate quartile of physical activity. Baseline subject characteristics were compared by analysis of variance for continuous variables and by the χ^2 test for dichotomous variables across quartiles. We used logistic regression analyses to examine the odds of cognitive decline (a decrease of ≥3 points on the mMMSE) as a function of physical activity quartile using the lowest quartile as a reference. We then adjusted the models for covariates that either were associated ($P<.05$) with physical activity quartile and with cognitive decline (age, educational level, depression, a history of hypertension or diabetes, estrogen use, and smoking) or could affect the ability to be physically active (baseline functional limitation, self-reported health status, and medical comordities such as a history of stroke or myocardial infarction). We also analyzed the odds of cognitive decline as a function of physical activity in subgroups of women (aged ≤70 or >70 years, educational level <12 or ≥12 years, and presence or absence of comorbid health conditions). Using the cognitive score as a continuous outcome, we determined if change in score (and percentage change of the initial score) on the mMMSE was associated with quartile of exercise (blocks walked or total kilocalories) using linear regression models. To determine if baseline physical performance could explain an association between exercise and cognitive decline, we also examined whether baseline walking speed was associated with cognitive decline using logistic regression. All significance levels reported are 2-sided, and all analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

physical activity quartile compared with the higher quartiles (25.1 ± 1.0 for the lowest quartile vs the second and third quartiles and 25.2 ± 0.9 for the highest quartile $P = .001$).

During the mean of 7.5 years of follow-up, women declined a mean ± SD of 1.0 ± 2.1 points on the mMMSE, and 1178 (20%) of the participants developed cognitive decline (≥3 points of decline on repeated mMMSEs). Twenty-four percent of the women in the lowest quartile of blocks walked per week developed cognitive decline compared with 17% of the women in the highest quartile ($P<.001$) (**Table 2**). Similarly, 24% of the women in the lowest quartile of total kilocalories expended per week developed cognitive decline vs 17% of the women in the highest quartile ($P<.001$). Compared with the lowest quartile, the odds of developing cognitive decline were 37% lower (odds ratio [OR], 0.63; 95% confidence interval [CI], 0.53-0.76) in the highest quartile of blocks walked and 35% lower (OR, 0.65; 95% CI, 0.54-0.78) in the highest quartile of total kilocalories expended. There was a significant trend for more exercise to be associated with a greater reduction of odds of cognitive decline ($P<.001$ for trend for quartiles of blocks walked and total kilocalories expended per week). Moreover, for every 10 blocks walked per day (approximately 1.6 km [1 mile]), women had a 13% (OR, 0.87; 95% CI, 0.82-0.92) lower odds of cognitive decline. For every SD (1700 kcal) of total kilocalories expended per week for physical activity, there was a 14% (OR, 0.86; 95% CI, 0.80-0.92) lower odds of cognitive decline. Compared with women without cognitive decline, women who developed cognitive decline on average were older (mean ± SD age, 72.2 ± 5.2 vs 70.4 ± 4.5 years; $P<.001$), were less educated (mean ± SD years of education, 12.6 ± 2.8 vs 13.0 ± 2.6; $P<.001$), had more symptoms of depression (mean ± SD, 1.6 ± 2.1 vs 1.4 ± 1.9 symptoms; $P<.001$), were more likely to have a history of hypertension (38% vs 35%; $P=.03$), were less likely to be taking oral estrogen replacement therapy (13% vs 16%; $P=.01$), and were less likely to smoke (7% vs 9%; $P=.009$).

After adjusting for baseline age, educational level, health status, functional limitation, depression score, stroke, diabetes, hypertension, myocardial infarction, smoking, and estrogen use, women with higher levels of physical activity remained at lower risk for cognitive decline (Table 2). To determine if baseline physical performance could have explained some of the association between exercise and cog-

Table 1. Baseline Characteristics of 5921 Women by Quartile of Total Kilocalories (Energy) Expended*

	Quartile†				
Characteristic	**Lowest (n = 1470)**	**Second (n = 1491)**	**Third (n = 1480)**	**Highest (n = 1480)**	***P*‡**
Age, mean ± SD, y	71.7 ± 5.2	70.6 ± 4.6	70.5 ± 4.6	70.2 ± 4.2	<.001
Education, mean ± SD, y	12.3 ± 2.5	12.8 ± 2.6	13.1 ± 2.7	13.4 ± 2.7	<.001
Excellent or good health	81	87	92	94	<.001
Medical history					
Stroke	2.5	1.1	1.6	1.8	.04
Myocardial infarction	7.6	5.1	3.8	4.1	<.001
Diabetes	8.5	4.6	4.6	4.1	<.001
Parkinson disease	0.8	0.3	0.3	0.3	.13
Hypertension	39.3	34.7	35.3	32.4	<.001
Depression score, mean ± SD§	1.9 ± 2.3	1.4 ± 1.9	1.2 ± 1.7	1.1 ± 1.6	<.001
Current estrogen use	13.4	14.2	15.3	18.3	<.001
Current smoker	11.2	9.8	8.0	6.7	<.001
Alcohol consumption, mean ± SD, drinks/wk	2.0 ± 4.4	1.9 ± 3.9	2.1 ± 4.0	2.3 ± 4.0	.05
Body mass index, mean ± SD‖	27.4 ± 4.9	26.3 ± 4.3	25.9 ± 4.1	25.5 ± 4.0	<.001
Functional limitation	3.5	0.9	0.6	0.3	<.001
Baseline mMMSE score, mean ± SD	25.1 ± 1.0	25.2 ± 1.0	25.2 ± 1.0	25.2 ± 0.9	.001

*Data are given as the percentage of women unless otherwise indicated. n = 5921 because 4 women did not provide information on total kilocalories expended per week. mMMSE indicates modified Mini-Mental State Examination.

†Quartiles indicate the range of energy expended: lowest, 0 to 615 kcal/wk; second, 616 to 1323 kcal/wk; third, 1324 to 2414 kcal/wk; and highest, 2415 to 17 531 kcal/wk.

‡Value from analysis of variance for continuous variables and from the χ^2 test for dichotomous variables.

§From the Geriatric Depression Scale–Shortened.

‖Calculated as weight in kilograms divided by the square of height in meters.

Table 2. Frequency of Cognitive Decline According to Physical Activity Quartile in 5925 Older Women*

			OR (95% CI)		
Physical Activity Quartile	**No. of Subjects**	**Cognitive Decline, %**	**Unadjusted**	**Age and Education Adjusted**	**Multivariate Adjusted†**
			Blocks Walked per Week		
Lowest	1450	24.0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Second	1438	21.6	0.87 (0.73-1.04)	0.87 (0.73-1.04)	0.87 (0.72-1.05)
Third	1581	17.6	0.68 (0.57-0.81)	0.70 (0.59-0.84)	0.63 (0.52-0.77)
Highest	1456	16.6	0.63 (0.53-0.76)	0.70 (0.58-0.84)	0.66 (0.54-0.82)
			Total Kilocalories (Energy) Expended per Week‡		
Lowest	1470	24.1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Second	1491	20.5	0.81 (0.69-0.96)	0.91 (0.76-1.08)	0.90 (0.74-1.09)
Third	1480	18.0	0.69 (0.58-0.83)	0.79 (0.66-0.95)	0.78 (0.64-0.96)
Highest	1480	17.0	0.65 (0.54-0.78)	0.77 (0.64-0.92)	0.74 (0.60-0.90)

*A complete description of the quartiles is given in the “Results” section of the text. OR indicates odds ratio; CI, confidence interval.

†Adjusted for baseline age, educational level, health status, functional limitation, depression score, stroke, diabetes, hypertension, myocardial infarction, smoking, and estrogen use.

‡n = 5921 because 4 women did not provide information on total kilocalories expended per week.

nitive decline, we examined whether baseline walking speed was associated with cognitive decline. In the age- and multivariate-adjusted models, quartile of baseline walking speed was not associated with risk of cognitive decline (for lowest quartile of walking speed: age-adjusted OR, 1.04 [95% CI, 0.87-1.25]; and multivariate-adjusted OR, 1.06 [95% CI, 0.86-1.30]).

To determine whether the association between physical activity and cognitive decline was consistent across subgroups of women with different propensities for exercise, we stratified the women into groups according to age (≤70 or >70 years), the presence or absence of comorbid medical conditions, and educational level (<12 or ≥12 years) (**Table 3**). Across all subgroups, women in the higher physical activity quartiles had lower odds of cognitive decline.

We also examined the association between physical activity quartiles and mMMSE score change (as a continuous variable). Quartile of blocks walked or total kilocalories expended was associated with 6- to 8-year change in mMMSE score (for quartile of blocks walked: regression coefficient, −0.14 [*P*<.001]; and for quartile of total kilocalories: regression coefficient, −0.08 [*P*<.001]). We calculated the percentage change in age-adjusted mMMSE score (as a function of baseline score) and found that women in the higher physical activity quartiles (measured by blocks walked) had less percentage decline during the 6 to 8 years compared with women in the lower quartiles (**Figure**).

Table 3. Odds of Cognitive Decline Associated With Physical Activity Quartile in Subgroups of Women

	Quartile*		
Subgroup	**Second**	**Third**	**Highest**
	Blocks Walked per Week		
Age, y			
≤70 (n = 3340)	0.67 (0.51-0.87)	0.61 (0.47-0.79)	0.55 (0.42-0.71)
>70 (n = 2585)	1.07 (0.83-1.35)	0.77 (0.60-0.98)	0.78 (0.60-1.01)
Comorbid medical conditions present			
Yes (n = 2300)	0.95 (0.72-1.24)	0.93 (0.71-1.23)	0.72 (0.54-0.95)
No (n = 2997)	0.83 (0.65-1.06)	0.49 (0.38-0.64)	0.58 (0.44-0.75)
Education, y			
<12 (n = 1033)	0.96 (0.67-1.38)	0.72 (0.49-1.05)	0.63 (0.41-0.96)
≥12 (n = 4891)	0.85 (0.70-1.04)	0.68 (0.55-0.83)	0.65 (0.53-0.80)
	Total Kilocalories (Energy) Expended per Week		
Age, y			
≤70 (n = 3337)	0.78 (0.60-1.02)	0.70 (0.54-0.92)	0.65 (0.50-0.86)
>70 (n = 2584)	0.91 (0.72-1.15)	0.77 (0.60-0.98)	0.74 (0.57-0.95)
Comorbid medical conditions present			
Yes (n = 2300)	0.96 (0.74-1.25)	0.68 (0.51-0.89)	0.73 (0.55-0.96)
No (n = 2996)	0.68 (0.53-0.88)	0.69 (0.53-0.89)	0.60 (0.46-0.78)
Education, y			
<12 (n = 1033)	1.06 (0.75-1.51)	0.96 (0.66-1.40)	0.52 (0.33-0.83)
≥12 (n = 4887)	0.76 (0.62-0.93)	0.66 (0.54-0.81)	0.69 (0.57-0.84)

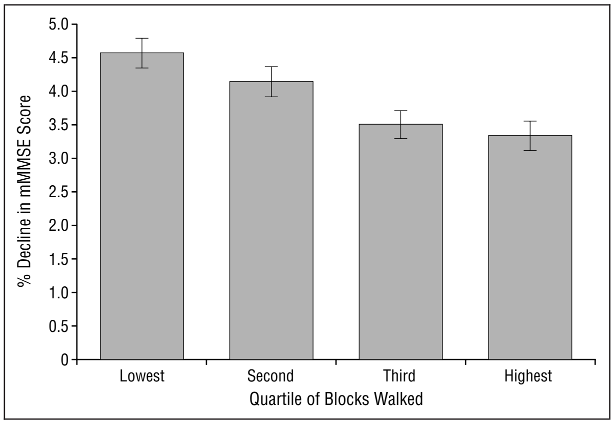
*Data are given as the odds ratio (95% confidence interval). The lowest quartile was used as a reference. A complete description of the quartiles is given in the "Results" section of the text.

COMMENT

In this prospective study of 5925 community-dwelling women, subjects with greater baseline physical activity, whether measured as blocks walked per week or as total kilocalories expended per week, were less likely to develop cognitive decline during the 6- to 8-year follow-up. This association remained after adjustment for covariates, including baseline functional and health status, and did not seem to be explained by differences in baseline physical performance measures. The strengths of our study are its large sample size and prospective design and the fact that we excluded subjects who had cognitive or physical limitations at baseline.

Our results are supported by several cross-sectional studies[5-9] in which elderly persons who were physically active performed better on cognitive testing compared with those who were inactive. One prospective study[10] has reported that strenuous, but not moderate, daily activities were associated with less cognitive decline in a healthy older cohort. We found that moderate, as well as strenuous, physical activity was associated with decreased risk. In our study, examples of moderate physical activity included playing 18 holes of golf once a week, playing tennis twice a week, or walking 1.6 km/d. Moderate levels of physical activity in elderly cohorts have also been shown to reduce mortality from coronary heart disease[19] and overall mortality,[20] to reduce the risk of osteoporotic fractures,[21] and to improve bone mineral density.[22]

Several trials,[23-25] most lasting several months, have failed to demonstrate a benefit of exercise interventions on cognitive function among older adults, while other trials[6,26-28] have found improved cognitive performance with physical activity. It is possible that physical activity may prevent cognitive decline but not improve cognitive performance during a short period in otherwise high-functioning elderly persons. This is plausible if physical activity–induced effects are associated with long-term protective benefits, such as a reduction in cardiovascular or cerebrovascular risk factors, but not in short-term effects. Regular physical activity may reduce serum lipid levels and hypertension and increase cardiovascular fitness,[3] all of which could reduce the risk of vascular dementia and Alzheimer disease.[29] Indeed, Rogers and colleagues[2] found that active elderly persons had less decline in cerebral blood flow during a 4-year period compared with less active elderly persons, a mechanism that might help maintain cognitive function. Another pos-



Percentage decline in age-adjusted modified Mini-Mental State Examination (mMMSE) score during the 6- to 8-year follow-up as a function of physical activity (blocks [1 block ≈ 160 m] walked). The median numbers (ranges) of blocks walked per week in the lowest, second, third, and highest quartiles were 7 (0-22), 28 (23-49), 77 (50-112), and 175 (113-672), respectively. The difference between women in the higher quartiles and those in the lower quartiles was significant (*P*<.001).

sible mechanism is that physical activity stimulates trophic factors and neuronal growth, possibly providing reserve against cognitive decline and dementia.[4,30] Finally, it may be that regular exercise is associated with a healthy lifestyle in general, and although we adjusted for several potential confounders, there may be other factors associated with healthy behavior in addition to physical activity that could in turn protect against cognitive decline.

Our study has several limitations. First, our measure of physical activity is based on a subject's self-report. While it is possible that some subjects may misreport their level of activity, the Paffenbarger Scale has been shown to be a reliable measure of physical activity in older women.[31] Second, while we used a conservative criterion of cognitive decline, defined as a 3-point decline or greater on the mMMSE, women did not undergo a clinical assessment for dementia and we cannot determine the cause of the cognitive decline. However, our finding of a 20% incidence of cognitive impairment over 8 years is similar to the 2% to 3% annual incidence of dementia reported for women in this age group.[16] Third, there was some attrition of study subjects between the first cognitive test and testing that was performed 6 to 8 years later. Women without follow-up were older, had lower baseline cognitive scores, and had lower baseline physical activity; exclusion of these subjects could lead to bias. Fourth, while we restricted our analyses to those without cognitive or physical impairment at baseline, it is possible that an association between subclinical cognitive impairment and physical activity level partially explains our results. Finally, most of the study subjects were white and we cannot conclude whether our findings would apply to other ethnic groups or to men.

We found that physical activity, even of a moderate degree, was associated with less risk of cognitive decline in older women followed up for 6 to 8 years. The exact mechanism of this association is not certain, although it may be related to a healthy lifestyle, a reduction in cardiovascular risk factors, or a direct effect on neurons. Further research is needed to determine if physical activity programs could prevent clinically significant cognitive impairment and if our findings can be replicated in other populations.

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