Physical Activity and Cognition in Women With Vascular Conditions

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Background: Individuals with vascular disease or risk factors have substantially higher rates of cognitive decline, yet little is known about means of maintaining cognition in this group.

Methods: We examined the relation between physical activity and cognitive decline in participants of the Women's Antioxidant Cardiovascular Study, a cohort of women with prevalent vascular disease or at least 3 coronary risk factors. Recreational physical activity was assessed at baseline (October 1995 through June 1996) and every 2 years thereafter. Between December 1998 and July 2000, a total of 2809 women 65 years or older underwent a cognitive battery by telephone interview, including 5 tests of global cognition, verbal memory, and category fluency. Tests were administered 3 additional times over 5.4 years. We used multivariable-adjusted general linear models for repeated measures to compare the annual rates of cognitive score changes across levels of total physical activity and energy expended in walking, as assessed at Women's Antioxidant Cardiovascular Study baseline.

Results: We found a significant trend ($P < .001$ for trend) toward decreasing rates of cognitive decline with increasing energy expenditure. Compared with the bottom quintile of total physical activity, significant differences in rates of cognitive decline were observed from the fourth quintile ($P = .04$ for the fourth quintile and $P < .001$ for the fifth quintile), or the equivalent of daily 30-minute walks at a brisk pace. This was equivalent to the difference in cognitive decline observed for women who were 5 to 7 years younger. Regularly walking for exercise was strongly related to slower rates of cognitive decline ($P = .003$ for trend).

Conclusion: Regular physical activity, including walking, was associated with better preservation of cognitive function in older women with vascular disease or risk factors.


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of vitamin E, vitamin C, and β-carotene supplementation for secondary prevention of CVD. Eligible participants were female health professionals at least 40 years old with 3 or more coronary risk factors (ie, diabetes mellitus, hypertension, hyperlipidemia, body mass index [calculated as weight in kilograms divided by height in meters squared] ≥30, or parental history of premature myocardial infarction) or CVD (ie, stroke, myocardial infarction, symptomatic angina pectoris, transient cerebral ischemia, or revascularization procedures, such as percutaneous transluminal angioplasty, coronary artery bypass graft, carotid endarterectomy, or peripheral artery surgery). In April 1998, a fourth study arm for B vitamin supplementation was added among 5442 women.19 Until July 2005, participants completed annual questionnaires on compliance, adverse effects, health and lifestyle, and clinical end points. None of the supplements used were associated with CVD recurrence16,17 or with cognitive change.16,17

COGNITIVE SUBCOHORT

Between July 1998 and December 2000, we assessed cognitive function by telephone interview among participants 65 years or older. Of 3170 eligible women, 190 were unreachable, 156 declined participation, and 2824 (94.8% of 2980 contacted women) completed the initial assessment. Participants received 3 follow-up assessments at 2-year intervals until July 2005; 92.5% completed at least 1 follow-up assessment, and 81.0% completed at least 3 assessments. For the fourth assessment, 24.3% were not contacted, as only a short interval had passed between their third interview and the end of the trial. We excluded 13 participants with prevalent Parkinson disease who likely had cognitive impairment and did not engage in regular physical activity. Therefore, the analyses included 2809 women. This study was approved by the institutional review board of Brigham and Women’s Hospital, Boston, Massachusetts.

PHYSICAL ACTIVITY ASSESSMENT

At baseline and biennially thereafter, women were asked about their mean weekly time spent during the past year on the following: walking or hiking; lap swimming; tennis, squash, or racquetball; jogging (speed ≥10-minute miles); running (speed ≥10-minute miles); bicycling, including the use of stationary machines; aerobic exercise, aerobic dance, or the use of exercise machines; and lower-intensity exercise, including yoga, stretching, or toning. We also inquired about the number of flights of stairs climbed daily (0, 1-2, 3-4, 5-9, 10-14, or ≥15) and the usual pace of walking (<3.2 km/h [≤2.0 mph, easy pace], 3.2-4.7 km/h [2.0-2.9 mph, normal pace], 4.8-6.3 km/h [3.0-3.9 mph, brisk pace], or ≥6.4 km/h [≥4.0 mph, very brisk pace]). We assigned each physical activity a metabolic equivalent of task (MET) value, where 1 MET is proportional to the energy expended while sitting quietly.16 MET values were 2 for running; 8 for stair-climbing; 7 for jogging, racquet sports, lap swimming, and bicycling; 6 for aerobic exercise, dance, or the use of exercise machines; and 4 for yoga, stretching, or toning. MET values for walking varied by pace, from 2.5 METs for an easy pace to 4.5 METs for a very brisk pace. For each physical activity, we estimated the energy expended in MET hours per week by multiplying its MET value by the duration. In a validation study among comparable female participants in a large cohort study,19 the physical activity responses given 2 years apart were reasonably correlated (r=0.6) given the expected true changes that might occur. Moreover, the physical activity recalled for the previous year correlated with activity based on past-week recalls (r=0.8) and activity diaries during the year (r=0.6).

COGNITIVE ASSESSMENT

Cognitive function was assessed by telephone interview using 5 tests. Global cognition was evaluated using the Telephone Interview for Cognitive Status (TICS),20 a telephone adaptation of the Mini-Mental State Examination (score range, 0-41 points). Verbal memory was assessed using the TICS 10-word list (immediate and delayed recalls) and the East Boston Memory Test (immediate and delayed recalls).21 Women were asked to name as many animals as possible in 1 minute in a test of category fluency.22

Our primary outcome was the rate of change in the global cognition composite score, computed as the mean of the z scores from all cognitive tests. As secondary outcomes, we considered the changes in TICS score, verbal memory composite score (mean of the verbal memory z scores), and category fluency score. Verbal memory is one of the best predictors of Alzheimer disease,23 and category fluency partly measures executive function, which is associated with vascular dementia.24,25 To derive the composite scores for 0.3% of participants who did not complete all tests, we used the means of the z scores from the available relevant tests.

In a validation study among 61 women, the global cognition composite score from the brief telephone-administered assessment correlated strongly with the total score from an extensive in-person interview for cognition (r=0.8). In a reliability study among 35 high-functioning educated women, the correlation between TICS scores administered twice 31 days apart was 0.7. Among 88 older female health professionals who were demographically similar to Women’s Antioxidant Cardiovascular Study participants, poor performances on the TICS and the verbal memory composite score were associated with significant 8- and 12-fold increases, respectively, in subsequent dementia diagnoses.26 Therefore, extensive evidence supports the validity of our telephone cognitive instrument.

COVARIATES

We considered several potential confounding factors plausibly linked with both physical activity and cognitive decline. Basic models included education and age at the initial cognitive assessment. Multivariable models further included the Women’s Antioxidant Cardiovascular Study randomization assignments, as well as numerous lifestyle and health variables listed in Table 1, with covariate specifications given in a footnote of Table 2.

STATISTICAL ANALYSIS

Physical Activity

We examined quintiles of total energy expended in all activities and quartiles of energy expended in walking (walking had a narrower distribution of energy expenditure), which was the most common physical activity. Before the first cognitive assessment, physical activity was assessed at randomization and again after 24 months. To reduce the effect of any recent changes in physical activity because of health or cognitive status (ie, reverse causation bias), our main analyses were based on the energy expenditures from the baseline questionnaire, which were assessed a mean of 3.5 years before the first cognitive assessment. However, given our interest in longer-term consistent physical activity levels, in secondary analyses we also examined the mean energy expenditures from reports on baseline and 24-month questionnaires. Furthermore, we examined associations among a subset of women whose physical activity
remained stable (ie, in the same or adjacent quintile at baseline and at 24 months).

When examining walking for exercise, we controlled for the energy levels expended in other activities as potential founders. To isolate the effects of walking, we also conducted a stratified analysis among 1387 women who only reported walking or engaging in low-intensity exercises for their activities.

Statistical Models

We used general linear models for repeated measures with random intercepts and slopes with an unstructured covariance matrix to estimate the association of physical activity with the annual rate of cognitive change. We assessed linear trends across physical activity categories by testing a continuous variable in which participants were assigned the median of the category. We used the Wald test for statistical testing. Models were fit by the maximum likelihood method using commercially available software (SAS, version 9.1; SAS Institute, Inc, Cary, North Carolina).

Because age, education, depression, diabetes, hypertension, or cardiovascular profile could modify the association between physical activity and cognitive decline, we evaluated 3-way interaction terms of time, physical activity level, and the potential effect modifier in separate multivariable-adjusted models. We performed an analysis that excluded women who had the worst cognitive function at the initial assessment (defined as the worst 10% of the distribution) to reduce any potential bias owing to less healthy behaviors or worse reporting in this group.

RESULTS

The mean time from the first physical activity assessment to the initial cognitive assessment was 3.5 years (range, 3.1-4.7 years), and the mean time from the initial cognitive assessment to the last cognitive assessment was 5.4 years (range, 4.0-6.1 years). Participants who were lost to follow-up tended to be older and less active at baseline.

Walking accounted for about half of the total energy expenditure (Table 1). Women with higher physical activity had lower mean body mass index, were more likely to consume alcohol, and were less likely to smoke or report lung disease, diabetes, or hypertension. Physical activity was not associated with CVD.

TOTAL PHYSICAL ACTIVITY

More active women tended to have better cognitive scores over time (Figure), and the difference in performance by physical activity level widened over time. In the basic and multivariable-adjusted models, greater physical
Table 2. Adjusted Differences in Annual Rates of Cognitive Change for Various Cognitive Scores Over 4 Assessments by Quintile of Total Physical Activity at Baseline Among 2809 Women in the Women’s Antioxidant Cardiovascular Study Cognitive Cohort

<table>
<thead>
<tr>
<th>Modela</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
<th>P Value for Trend</th>
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<tbody>
<tr>
<td></td>
<td>(n = 2809)</td>
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<tr>
<td>Global Cognition Score</td>
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<tr>
<td>Basic adjusted</td>
<td>0 [Reference]</td>
<td>0.00 (-0.01 to 0.02)</td>
<td>0.02 (0.00 to 0.04)</td>
<td>0.02 (0.00 to 0.04)</td>
<td>0.03 (0.01 to 0.05)</td>
<td>&lt;.001</td>
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<tr>
<td>Multivariable adjusted</td>
<td>0 [Reference]</td>
<td>0.00 (-0.01 to 0.02)</td>
<td>0.02 (0.00 to 0.04)</td>
<td>0.02 (0.00 to 0.04)</td>
<td>0.03 (0.01 to 0.05)</td>
<td>&lt;.001</td>
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<tr>
<td>Telephone Interview for Cognitive Status Score</td>
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<tr>
<td>Basic adjusted</td>
<td>0 [Reference]</td>
<td>-0.02 (-0.11 to 0.07)</td>
<td>0.05 (-0.04 to 0.15)</td>
<td>0.07 (-0.02 to 0.16)</td>
<td>0.09 (0.00 to 0.18)</td>
<td>.02</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>0 [Reference]</td>
<td>-0.01 (-0.10 to 0.08)</td>
<td>0.05 (-0.04 to 0.15)</td>
<td>0.07 (-0.02 to 0.17)</td>
<td>0.09 (-0.01 to 0.18)</td>
<td>.03</td>
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<td>Verbal Memory Score</td>
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<tr>
<td>Basic adjusted</td>
<td>0 [Reference]</td>
<td>0.00 (-0.02 to 0.02)</td>
<td>0.01 (-0.01 to 0.03)</td>
<td>0.03 (0.01 to 0.05)</td>
<td>0.03 (0.01 to 0.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multivariable adjusted</td>
<td>0 [Reference]</td>
<td>0.00 (-0.02 to 0.02)</td>
<td>0.01 (-0.01 to 0.03)</td>
<td>0.02 (0.00 to 0.05)</td>
<td>0.03 (0.01 to 0.05)</td>
<td>&lt;.001</td>
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<tr>
<td>Category Fluency Score</td>
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<td></td>
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<tr>
<td>Basic adjusted</td>
<td>0 [Reference]</td>
<td>0.04 (-0.08 to 0.17)</td>
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<td>0.02 (-0.10 to 0.15)</td>
<td>0.07 (-0.05 to 0.20)</td>
<td>.40</td>
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<td>0.05 (-0.08 to 0.18)</td>
<td>0.02 (-0.11 to 0.15)</td>
<td>0.08 (-0.05 to 0.21)</td>
<td>.40</td>
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</table>

a Basic adjusted model was adjusted for age at initial cognitive assessment (in years) and highest attained education (3 categories given in Table 1). Multivariable-adjusted model was further adjusted for the following: marital status (married, divorced, widowed, or single), alcohol intake (abstainer, 0.1-9.0 g/d, or >10 g/d), use of multivitamin supplements (yes or no), smoking status (never, past, or current), body mass index (in quartiles), postmenopausal hormone therapy use (never, past, or current), aspirin use exceeding 10 days in the previous month (yes or no), nonsteroidal anti-inflammatory drug use exceeding 10 days in the previous month (yes or no), history of depression (yes or no), lung disease (yes or no), joint pain or swelling (yes or no), arthritis (yes or no), cardiovascular profile at baseline (never, past, or current), aspirin use exceeding 10 days in the previous month (yes or no), nonsteroidal anti-inflammatory drug use exceeding 10 days in the previous month (yes or no), and randomization trial (myocardial infarction, stroke, revascularization procedure, symptomatic angina pectoris, transient cerebral ischemia, or no cardiovascular disease), diabetes mellitus (yes or no), hypertension (yes or no), or treatment, or yes without treatment), hyperlipidemia (no, yes on treatment, or yes without treatment), and randomization trial assignment for vitamin E (placebo or active), vitamin C (placebo or active), beta-carotene (placebo or active), and folate (not included, placebo, or active).

b Median (range) metabolic equivalent of task hours per week are 0.4 (<1.7) for the first quintile, 2.9 (1.7-4.6) for the second quintile, 7.5 (4.7-10.6) for the third quintile, 15.2 (10.7-21.2) for the fourth quintile, and 32.7 (>21.2) for the fifth quintile.

c Significant at α = .05.

Figure. Adjusted global cognition composite score (mean of z scores) during the cognitive follow-up period (1998-2005) by quintile of total physical activity at baseline (n = 2809). Trend curves are shown for quintiles 1, 3, and 5. For the fourth assessment, 24.3% of participants were not contacted, as only a short interval had passed between their third interview and the parent trial end; therefore, there is more statistical variation for this assessment.

Activity was significantly associated with slower declines in the global cognition score (P < .001 for trend), TICS (P = .03 for trend), and verbal memory score (P < .001 for trend) but was not associated with the category fluency score (Table 2). We found statistically significant differences in global cognitive decline beginning with women in the fourth (P = .04) and fifth (P < .001) quintiles of total energy expenditure, which was equivalent to walking 30 minutes or more every day at a brisk pace (ie, 5.5 km/h [3.5 mph]). Because the mean differences in cognitive decline can be difficult to interpret, we compared the estimates for physical activity and cognitive decline with those for age and cognitive decline; therefore, the effect of age on cognitive decline was used as a benchmark for interpretation. The mean difference in rates of cognitive decline between the first and fourth quintiles of physical activity was equivalent to the mean difference found for women 5 years apart in age, and the mean difference between the first and fifth quintiles was equivalent to 7 years of age. That is, the apparent cognitive benefits associated with physical activity levels, such as walking 30 minutes or longer every day at a brisk pace, were equivalent to being cognitively younger by 5 to 7 years.

In alternate analyses, when we considered the mean of the 2 physical activity measures before the first cognitive evaluation, the associations were similar and somewhat stronger, notably for the category fluency test: comparing the first quintile with the fifth quintile, the difference in annual cognitive decline was 0.03 standard units (95% confidence interval [CI], 0.01-0.05 standard units) for the global cognition score (P < .001 for trend), 0.12 points (95% CI, 0.03-0.22 points) for the TICS score (P = .03 for trend), 0.03 standard units (95% CI, 0.01-0.05 standard units) for the verbal memory score (P < .001 for trend), and 0.12 points (95% CI, -.01 to 0.25 points) for the category fluency score (P = .09 for trend). In addition, among the subset of 1971 women with stable physical activity levels on the 2 assessments before cognitive evaluations, results were also similar: comparing the first quintile with fifth quintile, the difference in annual cognitive decline was 0.04 standard units (95% CI, 0.01-0.06 standard units) for the global cognition score (P < .001 for trend), 0.13 points (95% CI, 0.02-
In models adjusted for other physical activities, we found significantly slower rates of decline in the global cognition, verbal memory, and category fluency scores associated with increased walking for exercise \( (P = .003, P = .01, \) and \( P = .03 \) for trend, respectively) (Table 3). However, significant associations were observed with the last quartile only (with a minimum of daily 30-minute walks), indicating a possible threshold effect. The mean difference in rates of cognitive decline between the first and fourth quartiles of walking was equivalent to being 5 to 7 years younger. Most important, the association with total physical activity was not restricted to women engaged in vigorous exercise; higher levels of walking for exercise were significantly related to less cognitive decline.

**WALKING**

In this large prospective study of women with preexisting CVD or vascular risk factors at high risk of cognitive decline, greater physical activity was associated with substantially slower cognitive decline. Participating in the 2 highest quintiles of physical activity was cognitively equivalent to being 5 to 7 years younger. Most important, the association with total physical activity was not restricted to women engaged in vigorous exercise; higher levels of walking for exercise were significantly related to less cognitive decline.

**COMMENT**

Strong evidence supports the hypothesis that physical activity, including walking, may prevent cognitive decline in generally healthy older adults. However, studies of those at increased risk of cognitive impairment have been scarce. Small clinical trials among participants with general cognitive impairments or with severe congestive heart failure found improvement or preservation of cognition in the physically active groups, but overall the definitions of high risk have been heterogeneous (eg, general cognitive problems rather than specific causes of cognitive impairments), yielding inconsistent and inconclusive results. Therefore, our findings provide important population-based long-term data that should be confirmed.

In our study, associations with change in category fluency score were less consistent than those for global cognition and verbal memory scores; this was also ob-
served in a cohort of healthy women.\textsuperscript{6} Category fluency score partially measures executive function, which is known to be affected by vascular disease.\textsuperscript{24,25} One could speculate that the indirect vasculoprotective effects are weaker than the direct neuroprotective effects in preserving cognition and that the domain most affected by vascular factors, such as executive function, may be less influenced than other domains. The potential differential associations with various cognitive domains are poorly understood. In addition, short-term intervention studies\textsuperscript{11,20-31} and large observational cohorts\textsuperscript{6,10,12} have revealed the possibility of differential effects with sex and various types of activities. These are important issues that need evaluation in future studies.

Our study had several strengths. Four successive cognitive assessments with high response rates were completed, maximizing information and minimizing biases because of loss to follow-up. Extensive health-related information was available, which allowed us to address confounding by baseline health status. Moreover, physical activity levels showed little variability according to baseline vascular disease, indicating low chance of confounding by severity of cardiovascular condition.

Some limitations should be considered. First, a telephone cognitive assessment might lack validity. However, reliability and validity studies of our telephone instrument provided convincing evidence of its usefulness to evaluate cognitive function in an epidemiologic study. Second, there may have been some misclassification of physical activity levels that were based on self-report. However, the physical activity questionnaire has been shown to reliably estimate physical activity levels,\textsuperscript{32} and misclassification would have led to biases toward the null. Third and most important, physical activity was assessed in late adulthood and may not reflect long-term exercise levels; it is also possible that inactivity or a sedentary lifestyle may represent preexisting cognitive impairment rather than a risk factor for its future development.\textsuperscript{32} We addressed this possible bias in several ways; we imposed a mean 3.5-year lag between report of physical activity and the initial cognitive assessment, and we conducted several secondary analyses among women whose activity levels were stable over the 2 assessments before the cognitive assessment and among women in the top 90th percentile at the first cognitive interview (ie, after excluding those more likely to have reduced physical activity or have errors in reporting activity because of cognitive impairment). Overall, we confirmed that higher levels of physical activity were consistently and significantly associated with less cognitive decline. We were unable to adjust for other potential confounders (eg, other psychiatric disorders or chronic kidney disease); therefore, some residual confounding by additional health or lifestyle factors is a possibility, and the results should be interpreted with appropriate caution. Fourth, our study population, which was composed of female health professionals with vascular conditions, may not allow for direct generalizability of the results to the general aging population. However, given that most of today’s older population has prevalent CVD (affecting \( \geq 70\% \) of those aged \( \geq 65 \) years in the United States\textsuperscript{5}), our study provides important evidence (which should be confirmed in other studies) of a modifiable risk factor for reducing cognitive impairment in this growing segment of the population.

Various biologic mechanisms may explain the positive relation between physical activity and cognitive health.\textsuperscript{33} Exercise may directly preserve neuronal structures by stimulating brain-derived neurotrophic factor and neuronal growth,\textsuperscript{34} possibly providing reserve against cognitive decline and dementia.\textsuperscript{35} Exercise may also have indirect effects by strengthening the underlying systems that support brain plasticity\textsuperscript{36,37} and helping to sustain the brain’s vascular health\textsuperscript{38} by beneficially influencing cardiovascular risk factors, promoting endothelial function, improving glucose and insulin regulation, and ensuring adequate cerebral perfusion.\textsuperscript{39} Furthermore, physical activity reduces inflammation, which is higher in those with vascular disease\textsuperscript{40,41} and impairs systemic and brain-specific growth factor signaling. Physical activity may also improve psychological well-being,\textsuperscript{42} which in turn may protect against decline in cognitive functioning.\textsuperscript{43}

In summary, we found clear and strong associations between greater physical activity and reduced cognitive decline in this population of women with vascular disease or coronary risk factors. If confirmed in future studies, physical activity recommendations could yield substantial public health benefits given the growing number of older persons with vascular conditions and their high risk of cognitive impairment.

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Author Contributions: Dr Kang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Vercambre, Grodstein, and Kang. Acquisition of data: Grodstein, Manson, and Kang. Analysis and interpretation of data: Vercambre, Grodstein, Manson, Stampfer, and Kang. Drafting of the manuscript: Vercambre. Critical revision of the manuscript for important intellectual content: Grodstein, Manson, Stampfer, and Kang. Statistical analysis: Vercambre. Obtained funding: Grodstein and Kang. Study supervision: Kang.

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