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Physical Activity, Including Walking, and Cognitive Function in Older Women

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Context Physical activity may help maintain cognitive function in older adults.

Objective To examine the relation of long-term regular physical activity, including walking, to cognitive function.

Design Women reported participation in leisure-time physical activities on biennial mailed questionnaires beginning in 1986. We assessed long-term activity by averaging energy expenditures from questionnaires in 1986 through participants' baseline cognitive assessments (1995 to 2001). We used linear regression to estimate adjusted mean differences in baseline cognitive performance and cognitive decline over 2 years, across levels of physical activity and walking.

Setting and Participants Nurses' Health Study, including 18766 US women aged 70 to 81 years.

Main Outcome Measure Validated telephone assessments of cognition administered twice approximately 2 years apart (1995 to 2001 and 1997 to 2003), including tests of general cognition, verbal memory, category fluency, and attention.

Results Higher levels of activity were associated with better cognitive performance. On a global score combining results of all 6 tests, women in the second through fifth quintiles of energy expenditure scored an average of 0.06, 0.06, 0.09, and 0.10 standard units higher than women in the lowest quintile (P for trend <.001). Compared with women in the lowest physical activity quintile, we found a 20% lower risk of cognitive impairment for women in the highest quintile of activity. Among women performing the equivalent of walking at an easy pace for at least 1.5 h/wk, mean global scores were 0.06 to 0.07 units higher compared with walking less than 40 min/wk ($P \leq .003$). We also observed less cognitive decline among women who were more active, especially those in the 2 highest quintiles of energy expenditure. Women in the fourth and fifth quintiles had mean changes in global scores that were 0.04 (95% confidence interval, 0.02-0.10) and 0.06 (95% confidence interval, 0.02-0.11) standard units better than those in the lowest quintile.

Conclusion Long-term regular physical activity, including walking, is associated with significantly better cognitive function and less cognitive decline in older women.

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The fastest growing age segment in the United States will soon be adults aged 65 years and older,[1] a group at high risk for developing dementia. Efforts to reduce dementia may be most successful at the earliest stages of disease development; subtle decrements in cognitive function predict dementia many years later and may be considered a marker of preclinical disease.[2-5] Thus, research on risk factors for diminished cognitive function in aging adults is of critical public health importance.

Accumulating evidence from animal[6-9] and human studies,[10-21] including small-scale clinical trials,[22] suggests that physical activity may reduce the risk of poor cognition and early cognitive decline. However, several issues have received limited consideration. Most important, the intensity of activity required to preserve cognitive function remains unclear. Walking is one of the most common[23] and among the most practical leisure-time activities practiced by older adults. Yet only 1 study has prospectively explored the potential benefits of walking on cognitive function, and in that study physical activity was assessed at only 1 point in time.[19] Thus, we examined physical activity, including walking, and cognitive function in a large cohort of older women.

METHODS

The Nurses' Health Study began in 1976 when 121 700 female registered nurses, aged 30 to 55 years and living in 11 US states, returned a mailed questionnaire about their medical history and health-related behaviors.[24] Since then, the women have completed questionnaires every 2 years; detailed items on physical activity were added begin-

See also p 1447.

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ning in 1986. To date, we have maintained follow-up of more than 90% of the original participants. This study was approved by the institutional review board of Brigham and Women's Hospital (Boston, Mass). Women gave informed consent to participate at the time of their cognitive assessment.

Study Population

From 1995 to 2001, we invited participants aged 70 years and older with no history of stroke to participate in a study of cognitive function. Of the 22715 women who were eligible, we were unable to contact 1031 (4.5%). Of those remaining, 7.7% refused to participate. After excluding women who were missing data on educational attainment or physical activity, women with Parkinson disease, and women unable to walk, our main analysis of physical activity and baseline cognitive function was based on 18766 women. Second cognitive assessments were administered a mean of 1.8 years (SD, 0.4) after baseline testing. Excluding those who died (n=15), to date we have attempted second assessments in 89% of participants in our baseline analysis. Of these, 99% completed a second assessment and 1.3% refused or were lost to follow-up. Thus, analyses of change in cognition included 16466 women.

Cognitive Function Assessment

All cognitive testing was administered using validated telephone interviews conducted by trained nurses. In the initial interview, we administered only the Telephone Interview for Cognitive Status (TICS)[25] and gradually added 5 more tests as participants' enthusiasm for cognitive testing became clear. Thus, the sample size differs somewhat across the cognitive tests, although participation rates remained identical for all tests, and there was no relation between physical activity and the number of tests administered.

The TICS (n=18766) is modeled on the Mini-Mental State Examination (MMSE). Brandt et al[25] reported a strong linear correlation between scores on the TICS and MMSE (Pearson correlation, 0.94), and high test-retest reliability. A test of delayed recall of the 10-word list from the TICS (n=16372) was 1 of the 5 tests added to our battery.

We also added the East Boston Memory Test (EBMT)[26,27] to assess immediate (n=18055) and delayed (n=18029) paragraph recall. We administered a test of category fluency in which participants were asked to name as many animals as they could in 1 minute[28] (n=18047). Finally, participants were administered the Digit Span Backwards test[29] (n=16382), which measures working memory and attention.

To summarize the overall association of physical activity with cognitive performance, for women given all 6 tests (n=16353) we constructed a global score by averaging the *z* scores from all tests. To assess overall verbal memory, a strong predictor of developing Alzheimer disease,[30] we combined the immediate and delayed recalls of the EBMT and the TICS 10-word list, for women given all 4 tests (n=16370), by averaging the *z* scores from these tests. Such composite scores are regularly used in published research on cognition[5,31] because they integrate information from a variety of sources and thus provide a more stable representation of cognitive function than a single test.

We extensively tested the reliability and validity of our telephone procedure for assessing cognition in high-functioning, educated women. We found high reliability of test performance among 35 women given the TICS twice, 31 days apart (test-retest correlation, 0.7, $P<.001$). In a validation study we conducted among 61 nuns from the Rush Religious Orders Study[5] of similar age and educational status to our participants, global scores from our brief telephone-administered cognitive assessment correlated highly with global scores from in-person interviews ($r=0.8$).

Physical Activity Assessment

Beginning in 1986, and again in 1988, 1992, and each subsequent biennial questionnaire, we requested detailed information on leisure-time physical activity. Women were asked to estimate the average amount of time per week during the past year spent on the following activities: running (≤10 min/mile); jogging (>10 min/mile); walking or hiking outdoors; racquet sports; lap swimming; bicycling; aerobic dance or use of exercise machines; other vigorous activities (eg, lawn mowing); and low-intensity exercise (eg, yoga, stretching, toning). Participants also indicated their usual outdoor walking pace: easy (>30 min/mile), normal (21-30 min/mile), brisk (16-20 min/mile), or very brisk (≤15 min/mile), and the number of flights of stairs climbed daily. We assigned each activity a metabolic equivalent value (MET) according to accepted standards,[32] where 1 MET is proportional to the energy expended while sitting quietly. MET values were 12 for running; 8 for stair-climbing; 7 for jogging, racquet sports, lap-swimming and bicycling; 6 for aerobic dance, use of exercise machines, and other vigorous activities; and 4 for yoga, stretching, or toning. MET values for walking varied by reported pace, from 2.5 METs for easy pace to 4.5 METs for very brisk pace. For each activity, we estimated the energy expended in MET-hours/wk, by multiplying its MET value by the time spent performing it.

In validation studies among women in the Nurses' Health Study II (a similar cohort of nurses), participants' responses, 1 year apart, to these questions on activity were reasonably correlated ($r=0.59$), given the expected true changes that might occur over a 1-year period.[33] Moreover, physical activity recalled for the previous year correlated strongly with past-week recalls of physical activity ($r=0.79$) and with physical activity logged in diaries during the year ($r=0.62$).

Statistical Analysis

Physical Activity. To assess long-term physical activity and to reduce the impact of any recent changes in activity due to health status (ie, "reverse causation" bias), our main analyses were based on the average of energy expenditures from the 1986 questionnaire through the questionnaire immediately preceding the baseline cognitive assessment. Thus, the averaged expenditures were calculated from a mean of 5 reports per woman over 8 to 15 years. The last reports of activity occurred, on average, 1.8 years prior to the baseline cognitive assessments. For analysis, we divided the averaged energy expenditures into quintiles.

Walking. In examining walking, we excluded women who reported participation in vigorous activities (6-MET intensity or greater), to disentangle the effects of walking from those of walking accompanied by more vigorous activity, leaving 7982 women for baseline analyses. Analyses of walking are based on average energy expended on walking from 1986 through the questionnaire immediately preceding the baseline cognitive assessment. Due to the smaller sample size in this analysis and the narrower distribution of energy expenditure in this group, we divided women into quartiles of walking expenditures rather than quintiles.

Statistical Models. We used multiple linear regression to compare mean baseline cognitive function and mean decline in cognitive performance over 2 years across categories of average physical activity and walking. We constructed 2 sets of models. In the first, we adjusted for factors that may confound the association between physical activity and cognition, including age at cognitive assessment, education (registered nurse degree, bachelor's degree, advanced graduate degree), husband's education (high school diploma or less, college degree, advanced graduate degree; an additional measure of socioeconomic status), alcohol consumption (measured using a food frequency questionnaire as none, up to 1 drink/week, 2-6 drinks/week, ≥1 drink/day), smoking (current, past, never), aspirin use (nonuser, 1 time/month to 2 times/week, ≥3 days/week), ibuprofen use (nonuser, current user), vitamin E supplementation (yes, no), antidepressant use (yes, no), poor mental health on the mental health scale of the Short Form-36 (SF-36), history of osteoarthritis, history of emphysema or chronic bronchitis, low vitality on the energy-fatigue scale of the SF-36, problems with balance, moderate to severe bodily pain,

Table 1. Characteristics of Women by Quintile of Overall Physical Activity*

	Quintile of Average Energy Expended (MET-hours/wk)†				
Characteristics	1 (<5.2) [n = 3720]	2 (5.2-10.0) [n = 3760]	3 (10.1-16.2) [n = 3750]	4 (16.3-26.0) [n = 3753]	5 (>26.0) [n = 3753]
Age at baseline cognitive assessment, mean (SD), y	74.3 (2.3)	74.2 (2.3)	74.2 (2.3)	74.2 (2.3)	74.2 (2.2)
Bachelor's, master's, or doctorate degree, No. (%)	712 (19)	766 (20)	842 (22)	859 (23)	1000 (27)
Husband has college education, No. (%)	1153 (42)	1348 (45)	1453 (48)	1539 (50)	1645 (54)
Alcohol intake, mean (SD), g/d	4.4 (10.0)	4.4 (8.5)	4.8 (8.7)	5.1 (9.1)	5.9 (8.9)
Smoking status, No. (%)					
Current	481 (13)	317 (8.4)	296 (7.9)	246 (6.6)	231 (6.2)
Past	1629 (43)	1685 (45)	1658 (44)	1776 (47)	1762 (47)
Regular aspirin use (≥3 times/wk), No. (%)	1261 (39)	1486 (43)	1516 (44)	1552 (44)	1463 (42)
Ibuprofen use (current), No. (%)	604 (16)	677 (18)	681 (18)	673 (18)	595 (16)
Vitamin E supplement use, No. (%)	1281 (42)	1552 (48)	1641 (51)	1672 (52)	1778 (55)
Antidepressant use, No. (%)	280 (7.5)	222 (5.9)	222 (5.9)	172 (4.6)	129 (3.4)
Self-reported balance problems, No. (%)	624 (17)	522 (14)	501 (13)	403 (11)	347 (9)
Health limits (at least a little) ability to walk a block, No. (%)	1113 (30)	634 (17)	481 (13)	369 (10)	240 (6)
Poor score on SF-36 energy fatigue scale, No. (%)‡	889 (29)	607 (18)	490 (14)	381 (11)	253 (7)
Poor score on SF-36 mental health scale, No. (%)‡	147 (4.7)	115 (3.4)	101 (3.0)	88 (2.6)	65 (1.9)
Self-reported health history, No. (%)					
Carotid endarterectomy	60 (1.6)	54 (1.4)	46 (1.2)	39 (1.0)	40 (1.1)
Coronary heart disease	257 (6.9)	265 (7.1)	220 (5.9)	208 (5.5)	179 (4.8)
Congestive heart failure	159 (4.2)	117 (3.1)	110 (2.9)	86 (2.3)	52 (1.4)
Transient ischemic attack	192 (5.1)	169 (4.5)	171 (4.6)	142 (3.8)	111 (3)
High blood pressure	2332 (62)	2145 (57)	2066 (55)	1967 (52)	1831 (49)
High cholesterol	2170 (58)	2268 (60)	2225 (59)	2190 (58)	2076 (55)
Diabetes	558 (15)	401 (11)	343 (9)	295 (8)	255 (7)
Emphysema or chronic bronchitis	433 (12)	308 (8.2)	299 (8)	259 (6.9)	226 (6)
Osteoarthritis	1722 (46)	1770 (47)	1746 (47)	1680 (45)	1574 (42)
Moderate to severe bodily pain	1381 (37)	1224 (33)	1156 (31)	1088 (29)	918 (24)

Abbreviation: MET, metabolic equivalent.
*Characteristics as of the questionnaire prior to cognitive assessment (see "Methods" section). Denominators for husband's education, alcohol intake, aspirin intake, vitamin E use, and SF-36 scores vary slightly from those shown.
†Average energy expenditure over the 8- to 15-year period prior to baseline cognitive assessment.
‡Poor score on the Short-Form 36 (SF-36) energy fatigue index is ≤55 of 100; poor score on the SF-36 mental health scale is ≤52 of 100.

and health limitations in walking a block. Adjustments for additional factors such as use of postmenopausal hormone therapy and apolipoprotein E ε4 did not alter the results and were not included in the final model.

In a second set of models, we added vascular factors that might be either confounders or intermediates in the causal pathway between physical activity and cognitive function, including high blood pressure, elevated cholesterol level, type 2 diabetes, coronary heart disease, coronary artery bypass graft surgery, congestive heart failure, transient ischemic attack, and carotid endarterectomy (women with stroke had already been excluded from participation in the baseline cognitive testing). Additionally, for our analyses of walking, we included terms for stair-climbing and other low-intensity activities. All information on potential confounding and intermediate variables was identified via the biennial questionnaires and women's status for each variable was considered through the questionnaire immediately preceding the cognitive assessment. Variables assessed multiple times were averaged for the model.

In analyses of cognitive decline, we adjusted for the covariates listed above, again with the status for each variable defined as of the questionnaire preceding the baseline cognitive assessment, as well as baseline cognitive test score.

To help interpret the mean differences in scores that we observed, we provide here the mean differences in cognitive scores that we found between different age groups, estimated from our multiple regression models, allowing a contrast of mean differences across age with mean differences across physical activity categories. For example, in our models, we found a mean difference of 0.08 standard units on the global score associated with each 2-year increment in age.

In additional analyses to help interpret clinical significance, we focused on participants in the lowest 10% of the distribution of cognitive performance. Such a population-based 10% cut-off point is a sensitive and specific marker of cognitive impairment[34] and has been used in other studies.[35-37] We computed adjusted prevalence odds ratios (ORs) of cognitive impairment using multiple logistic regression models including the potential confounding variables described above. We conducted analyses using SAS version 8.2 (SAS Institute Inc, Cary, NC) and $P<.05$ as the level of significance.

RESULTS

Physical Activity

A wide range of energy was expended on leisure-time activity (TABLE 1). Women were of similar age across quintiles of physical activity. Compared with women in lower quintiles of activity, women in higher quintiles were less likely to smoke and more likely to consume moderate levels of alcohol. As expected, women in higher quintiles were less likely to report problems with balance, health limitations in walking, and high levels of fatigue. Finally, as anticipated, cardiovascular disease, pulmonary disease, and diabetes were all less prevalent among more active women.

After adjusting for potential confounding factors, we found statistically significant trends of increasingly higher mean scores on all the cognitive measures with higher levels of long-term physical activity (TABLE 2). Further adjustment for vascular factors had little impact on these findings (data available from authors on request). Although the absolute differences in score may appear small, the mean differences we found across quintiles of physical activity were equivalent to the mean differences we observed for women 2 to 3 years apart in age. In addition, we found a significant association between physical activity and the odds of cognitive impairment. On the global score, women in the highest quintile of activity had 20% lower odds of cognitive impairment at baseline than women in the lowest quintile (OR, 0.80, 95% confidence interval [CI], 0.67-0.95).

We believe it is unlikely that women's health influenced their activity rather than the reverse, since we con-

Table 2. Mean Differences in Baseline Cognitive Function Scores by Quintile of Physical Activity*

Test	Quintile of Physical Activity					*P* Value for Trend
	1 (Lowest)	2	3	4	5 (Highest)	
TICS (n = 18 766)						
Adjusted mean difference (95% CI)	Reference	0.20 (0.07 to 0.32)	0.27 (0.15 to 0.40)	0.28 (0.15 to 0.40)	0.28 (0.21 to 0.47)	<.001
Category fluency (n = 18 047)						
Adjusted mean difference (95% CI)	Reference	0.59 (0.38 to 0.81)	0.74 (0.52 to 0.95)	0.76 (0.54 to 0.98)	0.95 (0.73 to 1.17)	<.001
Working memory and attention (n = 16 382)						
Adjusted mean difference (95% CI)	Reference	0.15 (0.03 to 0.27)	0.16 (0.04 to 0.28)	0.27 (0.15 to 0.39)	0.34 (0.22 to 0.46)	<.001
Verbal memory score (n = 16 370)†						
Adjusted mean difference (95% CI)	Reference	0.04 (0.01 to 0.07)	0.03 (0 to 0.07)	0.07 (0.04 to 0.10)	0.08 (0.05 to 0.12)	<.001
Global score (n = 16 353)†						
Adjusted mean difference (95% CI)	Reference	0.06 (0.03 to 0.09)	0.06 (0.03 to 0.09)	0.09 (0.06 to 0.12)	0.10 (0.07 to 0.13)	<.001

Abbreviations: CI, confidence interval; TICS, Telephone Interview for Cognitive Status.

*Mean differences are adjusted for age, education, husband's education, alcohol use, smoking status, aspirin use, ibuprofen use, vitamin E use, balance problems, health limitations in the ability to walk a block, osteoarthritis, emphysema or chronic bronchitis, fatigue, poor mental health (see Table 1), antidepressant use, and moderate to severe bodily pain.

†Verbal memory score averages performance in immediate and delayed 10-word recalls and immediate and delayed East Boston Memory Tests. Global score averages performance on all cognitive tests. Composite scores were computed only for women who completed all component tests.

sidered energy expenditures beginning when women were largely in their early 60s and ending 2 years prior to cognitive testing. Nonetheless, we conducted several alternative analyses to further address this issue. We examined physical activity reported at midlife by using questionnaire reports from only women aged 60 to 62 years between 1986 and 1988 (n=7907), and these results were similar (TABLE 3). In addition, in analyses excluding women reporting extremes of activity (eg, the least active quintile, the most active quintile) and in analyses excluding women with disabling symptoms and conditions (eg, pulmonary and cardiovascular disease, balance problems, and any reported health limitations in walking several blocks), the positive association between higher levels of physical activity and cognitive function persisted.

Walking

Among women who had not participated in vigorous activity, the quartiles of average energy expended on walking were less than 1.9 MET-hours/wk, 1.9 to 4.2, 4.3 to 8.5, and greater than 8.5. These cut points are approximately equivalent to walking at a pace of 21-30 min/mile for less than 38 min/wk, 38 minutes to 1.4 hours, 1.5 to 2.8 hours, and more than 2.8 h/wk. We found significantly higher cognitive scores for women in the third and fourth quartiles of walking on all our cognitive measures (TABLE 4). These findings are consistent with those for overall physical activity, which indicated significant associations between better cognitive performance and 5.2 or more MET-hours/wk of energy expenditure. In our data, differences in cognitive scores associated with walking at an easy pace for at least 1.5 h/wk (vs <38 min/wk) were equivalent to those we observed for women approximately 1.5 years apart in age.

Cognitive Decline

We found that regular physical activity was associated with less cognitive decline (TABLE 5). On almost all the cognitive measures higher levels of activity were associated with less cognitive decline, and aside from category fluency, these trends were significant at the $P<.001$ level. Results were gen-

Table 3. Mean Differences in Baseline Cognitive Function Scores by Quintile of Physical Activity Among Women Aged 60-62 Years (1986 or 1988)*

Test	Quintile of Physical Activity: 1 (Lowest)	2	3	4	5 (Highest)	P Value for Trend
TICS (n = 7907)						
Adjusted mean difference (95% CI)	Reference	0.27 (0.09 to 0.46)	0.43 (0.24 to 0.61)	0.43 (0.24 to 0.61)	0.51 (0.32 to 0.69)	<.001
Category fluency (n = 7828)						
Adjusted mean difference (95% CI)	Reference	0.28 (–0.05 to 0.61)	0.60 (0.27 to 0.93)	0.53 (0.20 to 0.86)	0.54 (0.22 to 0.87)	.01
Working memory and attention (n = 7454)						
Adjusted mean difference (95% CI)	Reference	0.13 (–0.04 to 0.30)	0.26 (0.09 to 0.44)	0.40 (0.23 to 0.58)	0.50 (0.32 to 0.67)	<.001
Verbal memory score (n = 7445)†						
Adjusted mean difference (95% CI)	Reference	0.06 (0.01 to 0.11)	0.06 (0.01 to 0.11)	0.08 (0.03 to 0.13)	0.10 (0.05 to 0.15)	.001
Global score (n = 7436)†						
Adjusted mean difference (95% CI)	Reference	0.06 (0.02 to 0.11)	0.09 (0.05 to 0.13)	0.11 (0.07 to 0.15)	0.11 (0.07 to 0.16)	<.001

Abbreviations: CI, confidence interval; TICS, Telephone Interview for Cognitive Status.
*Mean differences are adjusted for age, education, husband's education, alcohol use, smoking status, and aspirin use, as of the time of physical activity reporting.
†Verbal memory score averages performance in immediate and delayed 10-word recalls and immediate and delayed East Boston Memory Tests. Global score averages performance on all cognitive tests. Composite scores were computed only for women who completed all component tests.

Table 4. Mean Differences in Baseline Cognitive Function Scores by Quartile of Walking*

Test	Quartile of Walking (MET-hours/wk): 1 (<1.9)	2 (1.9-4.2)	3 (4.3-8.5)	4 (>8.5)	P Value for Trend
TICS (n = 7982)					
Adjusted mean difference (95% CI)	Reference	0.19 (0.02 to 0.36)	0.30 (0.13 to 0.47)	0.31 (0.13 to 0.48)	.003
Category fluency (n = 7674)					
Adjusted mean difference (95% CI)	Reference	0.28 (–0.01 to 0.57)	0.33 (0.03 to 0.63)	0.40 (0.10 to 0.70)	.03
Working memory and attention (n = 6968)					
Adjusted mean difference (95% CI)	Reference	0.14 (–0.02 to 0.30)	0.21 (0.04 to 0.37)	0.35 (0.18 to 0.51)	<.001
Verbal memory score (n = 6969)†					
Adjusted mean difference (95% CI)	Reference	0.03 (–0.02 to 0.08)	0.06 (0.01 to 0.10)	0.05 (0 to 0.10)	.07
Global score (n = 6957)†					
Adjusted mean difference (95% CI)	Reference	0.04 (0 to 0.08)	0.06 (0.02 to 0.10)	0.07 (0.02 to 0.11)	.007

Abbreviations: CI, confidence interval; MET, metabolic equivalent.
*Includes only the 7982 women who did not report any vigorous activity. Adjusted for the variables listed in the footnote to Table 2 as well as for MET-hours expended on stair-climbing and low-intensity exercise (eg, yoga, stretching, toning).
†Verbal memory score averages performance in immediate and delayed 10-word recalls and immediate and delayed East Boston Memory Tests. Global score averages performance on all cognitive tests. Composite scores were computed only for women who completed all component tests.

erally consistent in analyses in which we did not adjust for baseline cognitive performance and in analyses in which we excluded women who performed in the bottom 10% of a given cognitive measure at baseline (data available on request).

COMMENT

In this large, prospective study of older women, higher levels of long-term regular physical activity were strongly associated with higher levels of cognitive function and less cognitive decline. Specifically, the apparent cognitive benefits of greater physical activity were similar in extent to being about 3 years younger in age and were associated with a 20% lower risk of cognitive impairment. The association was not restricted to women engaging in vigorous activities: walking the equivalent of at least 1.5 hours per week at a 21-30 min/mile pace was also associated with better cognitive performance.

Several limitations to our study should be considered. In this observational study, results may be confounded by unmeasured factors. However, our homogeneous population of nurses minimizes the possibility that more active women had substantially better health care or health knowledge than less active women. Additionally, findings were robust to adjustments for numerous potential confounders, including a variety of health-related factors, and the apparent association between physical activity and cognition was consistent in analyses including only the healthiest participants with no reports of physically disabling conditions and symptoms.

Second, our findings could reflect "reverse causation," such that preexisting cognitive impairment caused a reduction in physical activity. Averaging reported physical activity levels over many years likely reduces this possibility; moreover, after imposing a minimum 9-year lag between the report of physical activity and the assessment of cognitive function, we still found a positive association between activity and cognition.

Our short follow-up period for measuring change in cognitive function is also a limitation. However, we initially collected information on physical activity 8 to 15 years prior to the baseline cognitive testing, and we were able to assess cognition among a large proportion of the women who provided data on their activity in 1986. Furthermore, our longitudinal results for cognitive decline over 2 years were entirely consistent with our findings for baseline cognition, with higher levels of activity strongly associated with less decline.

Finally, we did not assess development of dementia in our cohort. However, subtle decrements in cognition are a key predictor of dementia development[2-4] and may be considered a preclinical marker of early stages of dementia onset. In the Framingham study,[2] performance on tests of verbal memory predicted Alzheimer disease up to 22 years later: there was a 60% increase in risk for each standard deviation difference in baseline performance (relative risk, 1.57; 95% CI, 1.31-1.87). Over 6 years of follow-up in the Kungsholmen Project,[3] mean MMSE scores were 6.84 points lower at baseline for those who subsequently developed Alzheimer disease than those who did not, and those with poor performance on delayed verbal recall were 61% more likely to develop Alzheimer disease. Over 5 years of follow-up in the MoVIES study,[4] each standard deviation difference in decline in verbal memory was associated with a 2.5-fold higher rate of Alzheimer disease development. To evaluate this relation in our study, we administered the Dementia Questionnaire, a validated telephone informant interview for diagnosing dementia,[38] to 88 of our participants. An experienced neurologist from the Massachusetts Alzheimer Disease Research Center reviewed the findings, blinded to participants' cognitive testing. Over 3 years of follow-up, dementia diagnosis was nearly 8 times as likely among women who scored poorly on the TICS (OR, 7.6; 95% CI, 2.2-25), with a statistically significant, 11.6-fold increase for women performing poorly (defined as the lowest

Table 5. Mean Differences in Change in Cognitive Function Scores by Quintile of Physical Activity*

Test	Quintile of Physical Activity: 1 (Lowest)	2	3	4	5 (Highest)	*P* Value for Trend
TICS (n = 16 466)						
Adjusted mean difference (95% CI)	Reference	0.17 (0.05 to 0.30)	0.17 (0.04 to 0.29)	0.28 (0.15 to 0.41)	0.34 (0.21 to 0.47)	<.001
Category fluency (n = 15 835)						
Adjusted mean difference (95% CI)	Reference	0.04 (−0.16 to 0.25)	0.07 (−0.13 to 0.29)	0.18 (−0.03 to 0.39)	0.19 (−0.02 to 0.40)	.05
Working memory and attention (n = 14 376)						
Adjusted mean difference (95% CI)	Reference	0.12 (0.01 to 0.23)	0.13 (0.02 to 0.24)	0.20 (0.08 to 0.31)	0.25 (0.13 to 0.36)	<.001
Verbal memory score (n = 14 363)†						
Adjusted mean difference (95% CI)	Reference	0.04 (0 to 0.07)	0.01 (−0.02 to 0.04)	0.04 (0.01 to 0.08)	0.07 (0.04 to 0.11)	<.001
Global score (n = 14 344)†						
Adjusted mean difference (95% CI)	Reference	0.03 (0 to 0.05)	0.01 (−0.01 to 0.04)	0.04 (0.01 to 0.07)	0.06 (0.03 to 0.08)	<.001

Abbreviations: CI, confidence interval; TICS, Telephone Interview for Cognitive Status.
*Mean differences are adjusted for age, education, husband's education, alcohol use, smoking status, aspirin use, ibuprofen use, vitamin E use, balance problems, health limitations in the ability to walk a block, osteoarthritis, emphysema or chronic bronchitis, fatigue, poor mental health (see Table 1), antidepressant use, moderate to severe bodily pain, and baseline score.
†Verbal memory score averages performance in immediate and delayed 10-word recalls and immediate and delayed East Boston Memory Tests. Global score averages performance on all cognitive tests. Composite scores were computed only for women who completed all component tests.

10% of the distribution) on the verbal memory score.

Several mechanisms may potentially explain the relation between physical activity and cognitive function. Physical activity likely sustains the brain's vascular health by lowering blood pressure, improving lipoprotein profiles, promoting endothelial nitric oxide production,[39] and ensuring adequate cerebral perfusion.[40,41] Similarly, emerging evidence of a relation between insulin and amyloid β[42,43] (amyloid β plaques are a hallmark pathologic feature of Alzheimer disease) suggest that the benefits of aerobic activity on insulin resistance and glucose intolerance[44-46] may be another mechanism by which physical activity could prevent or delay cognitive decline. Physical activity may also directly affect the brain, potentially preserving neuronal structure and promoting the expansion of neural fibers, synapses, and capillaries.[41,47] In general, small clinical trials support cognitive benefits of physical activity,[22] yet due to practical limitations, it is difficult for trials to assess a wide variety of activities or long-term activity.

Large observational epidemiologic studies also suggest apparent benefits of physical activity on cognitive function. In particular, 4 large-scale prospective studies on this relation all have reported that greater activity is related to less cognitive decline.[13,16,17,19] The Study of Osteoporotic Fractures (SOF) is the only large-scale study that has examined walking in relation to cognitive decline.[19] Among 5925 women, aged 65 years and older, those who reported walking greater distances and those who were more physically active overall had smaller declines on the modified MMSE ($P<.001$ for both). Specifically, women in the highest quartile of walking distance (median, 175 blocks/wk) were 35% less likely (OR, 0.65; 95% CI, 0.54-0.78) than women in the lowest quartile (median, 7 blocks/wk) to experience cognitive decline over 6 to 8 years. These results were adjusted for numerous health indicators, including chronic diseases and functional limitations. Yet it remains possible that reverse causation explains some of the effects observed by all these studies. For example, in the SOF study, physical activity was first assessed at baseline, when half of the women were at least 70 years old and 43% had at least 1 confirmed health condition (eg, hypertension, diabetes, myocardial infarction). Thus, our findings serve as an important complement to the previous studies because our long-term follow-up and large sample size permit more detailed consideration of potential bias from a variety of health-related factors; for example, we examined activity reported at younger ages and considered numerous health-related exclusions.

In summary, in our study, as well as in other epidemiologic investigations, higher levels of physical activity, including walking, are associated with better cognitive function and less cognitive decline. Importantly, our data suggest that the apparent differences in cognition we observed between women with higher vs lower levels of activity were similar in magnitude to the differences in cognition we found among women 2 to 3 years apart in age.

Author Contributions: Dr Weuve had full access to all of 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: Weuve, Manson, Grodstein.
Acquisition of data: Manson, Grodstein.
Analysis and interpretation of data: Weuve, Kang, Manson, Breteler, Ware, Grodstein.
Drafting of the manuscript: Weuve.
Critical revision of the manuscript for important intellectual content: Weuve, Kang, Manson, Breteler, Ware, Grodstein.
Statistical analysis: Weuve, Kang, Ware, Grodstein.
Obtained funding: Ware, Grodstein.
Administrative, technical, or material support: Manson.
Study supervision: Manson, Grodstein.

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> The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.
>
> —Sir William Bragg (1862-1942)