

Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer Disease

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ALZHEIMER DISEASE (AD) IS THE leading cause of dementia in older persons, but few risk factors for the disease have been identified. Frequent participation in cognitively stimulating activities has been hypothesized to reduce risk of AD,¹⁻³ but this hypothesis has not been tested prospectively in longitudinal studies of incident disease. Support for the hypothesis now comes mainly from retrospective case-control studies suggesting that mid-life cognitive activity is associated with disease risk^{4,5} and from cross-sectional research showing an association between frequency of cognitive activity and level of cognitive function in old age.⁶⁻⁸ In the current study, we used a previously established measure of frequency of participation in common cognitive activities⁸ and tested its association with incident AD and decline in cognitive function in a large cohort of older Catholic clergy members examined annually for up to 7 years.

METHODS

Participants

All subjects are participants in the Religious Orders Study, an ongoing lon-

Context Frequent participation in cognitively stimulating activities has been hypothesized to reduce risk of Alzheimer disease (AD), but prospective data regarding an association are lacking.

Objective To test the hypothesis that frequent participation in cognitive activities is associated with a reduced risk of AD.

Design Longitudinal cohort study with baseline evaluations performed between January 1994 and July 2001 and mean follow-up of 4.5 years.

Participants and Setting A total of 801 older Catholic nuns, priests, and brothers without dementia at enrollment, recruited from 40 groups across the United States. At baseline, they rated frequency of participation in common cognitive activities (eg, reading a newspaper), from which a previously validated composite measure of cognitive activity frequency was derived.

Main Outcome Measures Clinical diagnosis of AD by a board-certified neurologist using National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria and change in global and specific measures of cognitive function, compared by cognitive activity score at baseline.

Results Baseline scores on the composite measure of cognitive activity ranged from 1.57 to 4.71 (mean, 3.57; SD, 0.55), with higher scores indicating more frequent activity. During an average of 4.5 years of follow-up, 111 persons developed AD. In a proportional hazards model that controlled for age, sex, and education, a 1-point increase in cognitive activity score was associated with a 33% reduction in risk of AD (hazard ratio, 0.67; 95% confidence interval, 0.49-0.92). Results were comparable when persons with memory impairment at baseline were excluded and when terms for the apolipoprotein E ϵ 4 allele and other medical conditions were added. In random-effects models that controlled for age, sex, education, and baseline level of cognitive function, a 1-point increase in cognitive activity was associated with reduced decline in global cognition (by 47%), working memory (by 60%), and perceptual speed (by 30%).

Conclusion These results suggest that frequent participation in cognitively stimulating activities is associated with reduced risk of AD.

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gitudinal clinical-pathological study of aging and AD. Older Catholic nuns, priests, and brothers were recruited from about 40 groups across the United States (see Acknowledgment). The study was approved by the Human Investigations Committee of Rush-Presbyterian-St. Luke's Medical Cen-

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ter. Eligibility was established at baseline and required an age of 65 years or older, absence of a clinical diagnosis of dementia, and consent to annual clinical evaluations and to brain donation at the time of death.

At baseline, each person had a uniform structured evaluation that was repeated annually by examiners blinded to previously collected data. The evaluation has been previously described.⁹⁻¹¹ It included a medical history, neurological examination, assessment of cognitive function, and review of brain scan when available. On the basis of this evaluation, a board-certified neurologist diagnosed AD and other common conditions affecting cognitive or physical function (eg, stroke). The diagnosis of AD followed the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA).¹² These criteria require a history of cognitive decline and impairment in memory and at least 1 other cognitive domain. Some persons who met these criteria had another condition impairing cognition (termed "possible" AD in the NINCDS/ADRDA system). Because exclusion of this subgroup did not affect results, it is included in all analyses reported in this article.

Of 1003 persons who expressed interest after a presentation about the Religious Orders Study, 879 agreed to participate and had a baseline evaluation between January 1994 and July 2001. We excluded 74 persons who met criteria for dementia at baseline and 4 persons with missing diagnostic or cognitive activity data. Of the remaining 801 persons, 21 died before the first follow-up evaluation and 40 had not yet reached the date of their first follow-up. Of the remaining 740 persons, follow-up information on AD was available in 733 (99%), with a mean of 5.5 evaluations per person (range: 2-8); follow-up composite cognitive scores were available in 724 (98%), with a mean of 5.4 valid scores per individual (range: 2-8). Analyses are based on these per-

sons. Nearly all of them were still active in their order, parish, or community at baseline, and 70% were working at least part-time.

Assessment of Cognitive Activity

We used a previously established, composite measure of cognitive activity frequency in analyses.⁸ At baseline, persons were asked about time typically spent in 7 common activities that involve information processing as a central component: viewing television; listening to radio; reading newspapers; reading magazines; reading books; playing games such as cards, checkers, crosswords, or other puzzles; and going to museums. Frequency of participation in each activity was rated on a 5-point scale, as follows: 5 points, every day or about every day; 4 points, several times a week; 3 points, several times a month; 2 points, several times a year; and 1 point, once a year or less. Responses to each item were averaged to yield the composite measure.

We used a composite measure to reduce floor and ceiling artifacts and other sources of measurement error. As previously described, it was formed by averaging responses to each item rather than weighting items by the estimated cognitive demand involved in the activity because the latter approach yielded a composite measure that was indistinguishable from a composite based on frequency alone.⁸ In a geographically defined population of older persons, each item was positively correlated with the total score on the other 6 (range: 0.8-0.46, all $P < .01$), supporting the use of a composite measure. This composite measure had positive correlations of moderate size with educational attainment and a performance-based measure of cognitive function, supporting its construct validity.

Assessment of Cognitive Function

At each evaluation, 20 cognitive tests were administered in an approximately 45-minute session. One test, the Mini-Mental State Examination (MMSE¹³) was used only for descriptive purposes. There were 7 tests of epi-

sodic memory: immediate and delayed recall of the East Boston Story,¹⁴ Logical Memory Ia and IIa,¹⁵ and Word List Memory, Recall, and Recognition¹⁶; 4 tests of semantic memory: Boston Naming Test,¹⁶ Extended Range Vocabulary,¹⁷ Verbal Fluency,¹⁶ and National Adult Reading Test¹⁸; 4 tests of working memory: Digits Forward and Digits Backward,¹⁵ Digit Ordering,¹⁹ and Alpha Span²⁰; 2 tests of perceptual speed: Symbol Digit Modalities Test²¹ and Number Comparison¹⁷; and 2 tests of visuospatial ability: Judgment of Line Orientation²² and Standard Progressive Matrices.²³ Composite measures of global cognition, based on all 19 tests, and of the specific domains of cognitive function defined above were used in analyses. Each measure was formed by converting raw scores on component tests to z scores, using the baseline mean and SD and computing the average. Detailed information about the individual tests and summary measures is published elsewhere.¹¹

Collection of Other Data

We assessed participation in physical activities with questions adapted²⁴ from the 1985 Health Interview Survey.²⁵ The activities were walking for exercise, gardening or yardwork, calisthenics or general exercise, bicycle riding, and swimming or water exercise. Persons were asked if they had participated in each activity in the last 2 weeks, and if so, the number of occasions and average minutes per occasion. Minutes in each activity were summed and divided by 120 to yield a composite measure of participation in physical activity expressed as hours per week. Because results were unchanged when activities were weighted by the estimated energy expended,²⁶ we used total weekly hours in all analyses. Due to its skewed distribution, we treated it as a categorical variable in the main analysis with people grouped into quartiles.

Apolipoprotein E (ApoE) genotyping was performed by an investigator blinded to all clinical data. Blood was collected at each participating Reli-

Table 1. Baseline Characteristics of Religious Orders Study Participants Who Did and Did Not Develop Alzheimer Disease (AD)*

Characteristic	Developed AD (n = 111)	Did Not Develop AD (n = 622)	P Value
Age, y	81.1 (6.2)	74.3 (6.3)	<.001
Women, %	66.7	67.2	.91
White, non-Hispanic, %	94.6	90.4	.21
Years of education	18.1 (3.6)	18.2 (3.2)	.86
Cognitive activity score†	3.46 (0.59)	3.59 (0.53)	.02
MMSE score	27.1 (2.2)	28.7 (1.4)	<.001
Global cognition score	-0.356 (0.444)	0.188 (0.457)	<.001
Episodic memory score	-0.435 (0.661)	0.237 (0.540)	<.001
Semantic memory score	-0.262 (0.696)	0.174 (0.647)	<.001
Working memory score	-0.328 (0.640)	0.155 (0.662)	<.001
Perceptual speed score	-0.519 (0.827)	0.234 (0.801)	<.001
Visuospatial ability score	-0.290 (0.741)	0.163 (0.805)	<.001

*All data are presented as mean (SD) unless otherwise indicated. MMSE indicates Mini-Mental State Examination.
†Cognitive activity scores ranged from 1.57-4.71 (possible range: 1-5).

gious Orders Study site with acid citrate dextrose anticoagulant and stored at room temperature. It underwent lymphocyte separation within 24 hours of collection. DNA was extracted from approximately 2 million to 3 million cells and amplified by the polymerase chain reaction as described by Hixson and Vernier.²⁷ Of 801 eligible persons at baseline, ApoE genotype was available in 721 (90%), and 186 (26%) had at least 1 $\epsilon 4$ allele.

Seven medical conditions were identified in at least 5% of study participants at baseline. Classification of 6 was based on medical history: hypertension, diabetes, heart disease, cancer, thyroid disease, and head injury with loss of consciousness. A clinical diagnosis of stroke was made in 53 persons (7%) based on history, examination, and in 31 of these, review of a prior brain scan (with evidence of cerebrovascular disease in 18). The number of these conditions present at baseline was used in analyses.

Depressive symptoms were assessed at baseline with a 10-item form²⁸ of the Center for Epidemiologic Studies Depression Scale.²⁹ The score was the number of symptoms experienced in the past week.

Data Analysis

The association of cognitive activity with risk of developing AD was as-

sessed in a Cox proportional hazards model, adjusted for the potentially confounding effects of age, sex, and education.³⁰ In additional models, we excluded persons with low episodic memory scores at baseline and added terms for the presence of at least 1 ApoE $\epsilon 4$ allele and for the number of medical conditions and depressive symptoms at baseline.

We used random-effects regression models to assess the relation of cognitive activity with baseline level of cognitive function and annual rate of change.³¹ Each cognitive function measure was analyzed in a model with terms for cognitive activity, time, and their interaction, and for the potentially confounding effects of age, sex, and education. The term for cognitive activity indicates the mean difference in cognitive function at baseline associated with a 1-point increase in cognitive activity. The term for time indicates the average rate of cognitive change per year in a typical participant with a cognitive activity score of 3, and the interaction term indicates the effect of a 1-point change in cognitive activity on annual rate of cognitive change. Further description of the application of these models to cognitive function data is provided elsewhere.^{11,32}

Comparable analyses were used to examine the relation of the physical activity measure with incident AD and

change in cognitive function. Model assumptions were assessed graphically and analytically and were found to be adequately met. All analyses were carried out in SAS.³³ A P value of less than .05 was considered significant.

RESULTS

Cognitive Activity and Incident AD

Scores on the composite measure of cognitive activity ranged from 1.57 to 4.71 (mean, 3.57; SD, 0.55), with higher scores indicating more frequent activity. Cognitive activity had modest correlations with age (r , -0.08; P < .05) and education (r , 0.20; P < .01) but was not associated with sex ($t_{799} = 0.35$, $P = .73$).

Participants were followed up for a mean of 4.5 years. A total of 111 persons developed AD after a mean of 3.0 years; 101 met NINCDS/ADRDA criteria for probable AD and 10 for possible AD (because of cognitive impairment due to stroke in 5 and to Parkinson disease in 5). Baseline characteristics of these persons and of those who did not develop AD are shown in TABLE 1. Of the 111 persons in the incident disease group, 51 have died. Brain autopsy results are available for 31, of whom 26 (84%) met Consortium to Establish a Registry for Alzheimer's Disease pathological criteria for AD (14 definite, 12 probable) based on ratings of neuritic plaque density in 3 neocortical regions.³⁴

Three persons with dementia due to other causes were excluded from analyses of disease incidence. In a proportional hazards model that adjusted for age, sex, and education, the relative risk (RR) of developing AD decreased by 33% (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.49-0.92) for each 1-point increase in the composite measure of cognitive activity (TABLE 2). Thus, compared with a person with activity frequency at the 10th percentile (score = 2.86), the RR of disease was reduced by 28% in a person whose cognitive activity frequency was at the 50th percentile (score = 3.71) and by 47% in a person whose activity frequency was at the 90th percentile (score = 4.29). Education was not

related to disease risk in this model (HR, 1.02; 95% CI, 0.96-1.08) or when the analysis was repeated without cognitive activity (HR, 1.01; 95% CI, 0.95-1.07).

We next considered whether the results depended on a subgroup with manifestations of early AD. Because episodic memory impairment has been shown to be a very early sign of disease,^{35,36} we repeated the analysis excluding 35 persons with a baseline episodic memory score at or below the fifth percentile, and the association of cognitive activity with incident AD remained (HR, 0.59; 95% CI, 0.41-0.86). Results were comparable when we excluded those at or below the 10th percentile (n=69) (HR, 0.57; 95% CI, 0.38-0.85) or 15th percentile (n=104) (HR, 0.58; 95% CI, 0.38-0.88).

Because the ApoE $\epsilon 4$ allele is an established risk factor for AD, we repeated the analysis with a term for possession of 1 or more $\epsilon 4$ alleles. The association of cognitive activity remained significant in this model (HR, 0.67; 95% CI, 0.49-0.92), and in a subsequent model, there was no interaction of $\epsilon 4$ with cognitive activity ($P=.90$).

We also examined whether other medical conditions or depression influenced the association of cognitive activity with AD. We added terms to the core model for the number of common medical conditions (mean, 1.1; range: 0-6) and number of depressive symptoms (mean, 1.0; range: 0-8) at baseline, and results were not substantially changed (HR for cognitive activity, 0.70; 95% CI, 0.51-0.97).

Cognitive Activity and Change in Cognitive Function

Another way to assess the impact of pre-existing cognitive impairment on results is to examine the association of cognitive activity with the principal manifestation of AD, cognitive decline, while controlling for baseline level of cognition. We did this in a series of random-effects models that examined the relation of cognitive activity with baseline level of and annual rate of change in cognitive function. Each

model included terms to control for the potentially confounding effects of age, sex, and education. To make use of all available data, the initial analysis used the global measure of cognition, which ranged from -1.765 to 1.374 at baseline, with higher scores indicating better function. At baseline, each point of cognitive activity score was associated with 0.128 units in the global cognitive score ($P<.001$). On average, the global cognitive score declined 0.043 units per year ($P<.001$), and this rate decreased by 0.020 units ($P<.05$), or about 47%, for each 1-point increase in cognitive activity score. Thus, on average, a person with activity frequency at the 10th percentile declined 0.046 units per year in global cognition; this rate was reduced by 0.014 units (about 30%) for an activity frequency score at the 50th percentile and by 0.026 units (about 60%) for an activity frequency score at the 90th percentile.

To determine whether cognitive activity was related to decline in some domains of cognition but not others, we repeated the analysis using measures of function in specific cognitive domains (TABLE 3). More frequent cognitive activity was associated with higher baseline function in each cognitive domain. On average, performance declined in

each cognitive domain, as shown by the terms for time. In addition, cognitive activity was associated with lower rates of decline in working memory, by 0.021 units or about 60% for each 1 point of cognitive activity score, and perceptual speed, by 0.026 units or about 30%, and a trend toward reduced decline in episodic memory. By contrast, change in semantic memory and visuospatial ability was not significantly related to cognitive activity.

Physical Activity, Incident AD, and Change in Cognitive Function

To determine whether the effect of cognitive activity reflected a nonspecific effect of activity, we also examined the association of physical activity with risk of disease. At baseline, persons spent a median of 3.5 hours per week in

Table 2. Relative Risk of Incident Alzheimer Disease Associated With Age, Sex, Education, and Cognitive Activity Frequency, Estimated From a Proportional Hazards Model

Model Terms*	Relative Risk (95% Confidence Interval)
Age	1.14 (1.11-1.18)
Male sex	1.35 (0.89-2.04)
Education	1.02 (0.96-1.08)
Cognitive activity score	0.67 (0.49-0.92)

*Relative risk is for a 1-year increase in age (range: 65-98 years) and in education (range: 6-30 years) and a 1-unit increase in cognitive activity score (range: 1.57-4.71).

Table 3. Summary of Random-Effects Models of the Association of Cognitive Activity Frequency With Baseline Level of and Annual Rate of Change in Specific Cognitive Functions*

Cognitive Measure	Model Terms	Estimate (SE)	P Value
Episodic memory	Cognitive activity	0.100 (0.037)	.007
	Time	-0.037 (0.008)	<.001
	Cognitive activity \times time	0.020 (0.012)	.10
Semantic memory	Cognitive activity	0.221 (0.038)	<.001
	Time	-0.048 (0.007)	<.001
	Cognitive activity \times time	0.010 (0.010)	.36
Working memory	Cognitive activity	0.082 (0.041)	.05
	Time	-0.035 (0.005)	<.001
	Cognitive activity \times time	0.021 (0.008)	.007
Perceptual speed	Cognitive activity	0.211 (0.052)	<.001
	Time	-0.087 (0.008)	<.001
	Cognitive activity \times time	0.026 (0.012)	.02
Visuospatial ability	Cognitive activity	0.133 (0.048)	.005
	Time	-0.020 (0.007)	.002
	Cognitive activity \times time	0.015 (0.010)	.14

*Results show the effect of a 1-unit change in the cognitive activity score. Age, sex, education, and their interactions with time (measured in years) were also adjusted for in each model.

Table 4. Relative Risk of Incident Alzheimer Disease Associated With Age, Sex, Education, and Physical Activity Frequency, Estimated From a Proportional Hazards Model*

Model Terms	Relative Risk (95% Confidence Interval)
Age	1.15 (1.11-1.18)
Male sex	1.46 (0.95-2.23)
Education	1.01 (0.95-1.07)
Physical activity	
Quartile 2	0.71 (0.42-1.19)
Quartile 3	0.73 (0.44-1.20)
Quartile 4	0.61 (0.35-1.05)

*Relative risk is for a 1-year increase in age (range: 65-98 years) and in education (range: 6-30 years). For physical activity, the least active quartile was the reference group for comparisons with each of the other quartiles.

physical activities (interquartile range, 0.5-7.0; mean, 5.7; SD, 8.3 hours). Because of the skewed distribution, we divided physical activity time into quartiles and contrasted those in the lowest quartile with each of the remaining quartiles in a proportional hazards model that controlled for age, sex, and education. As shown in TABLE 4, risk of incident AD was not significantly reduced in any quartile relative to the lowest quartile. Similar results were obtained when the analysis was repeated with physical activity treated as a continuous variable (HR, 1.00; 95% CI, 0.97-1.02). Results were also comparable when cognitive activity was added to the model. In random-effects models that controlled for demographic variables, physical activity was not related to decline in global or specific measures of cognitive function.

COMMENT

We found that frequency of participation in common cognitive activities was associated with incident AD during a mean of 4.5 years of follow-up. On average, a person reporting frequent cognitive activity at baseline (90th percentile) was 47% less likely to develop AD than a person with infrequent activity (10th percentile). These results suggest that frequent cognitive activity in old age is associated with reduced risk of incident AD.

A prospective, population-based study found that lower participation in several leisure activities was associ-

ated with higher risk of incident dementia after 3 years of follow-up.³⁷ However, few of the activities were cognitive, activity frequency was not assessed, and education was not controlled for. In 2 retrospective case-control studies, frequency of cognitive and physical activity in mid-life was associated with risk of AD.^{4,5} However, information about mid-life activity was obtained after disease onset, by informant-report for cases, and by self-report for controls, potentially biasing results.

Few prospective studies have evaluated the relation of physical activity to dementia or AD, and their results have been inconsistent.³⁸⁻⁴⁰ We found no evidence that frequency of participation in physical activities was associated with risk of AD or rate of cognitive decline. This observation is important because it suggests that the association of cognitive activity with disease risk reflects mental stimulation rather than a nonspecific result of being active.

A novel feature of this study is that incident AD and change in different cognitive abilities were used as separate but complementary outcomes. We found that the frequency of cognitive activity was not only associated with level of cognition at baseline, consistent with prior research,⁶⁻⁸ but also with rate of cognitive decline, suggesting that the association of cognitive activity with AD is not exclusively due to the association of cognitive activity with premorbid level of cognitive ability, a known risk factor for the disease.^{41,42} A previous study found that frequency of novel information processing was associated with rate of cognitive decline during a 6-year period.⁴³ This association was observed for only 1 of 9 cognitive measures, however, and education was not controlled for.

The basis of the association of cognitive activity with incident AD is uncertain. One hypothesis is that cognitive activity is protective.¹⁻³ One version of this hypothesis is that with repetition some cognitive skills

become more efficient and less vulnerable to disruption by AD pathology.⁴⁴ Alternatively, frequent cognitive activity may strengthen processing skills such as working memory and perceptual speed, which may help to compensate for age-related decline in other cognitive systems.⁴⁵ That cognitive activity was mainly associated with change in working memory and perceptual speed in this study, and with working memory in a prior study,⁴³ is consistent with a compensatory mechanism.

Another possibility is that reduced cognitive activity is an early sign of AD. However, we excluded persons who met clinical criteria for AD at baseline and obtained comparable results in secondary analyses after excluding those with low episodic memory scores at baseline. Further, cognitive activity was related to rate of cognitive decline after controlling for baseline level of cognition. Nevertheless, because AD is thought to develop slowly over many years, it is possible that prodromal manifestations of the disease contributed to the results. Indeed, if cognitive activity is protective, reduced cognitive activity should be an early sign of disease.

Cognitive activity may also be a proxy for some other less easily modified variable. However, we controlled for key demographic and clinical variables that have been associated with disease risk, cognitive activity frequency, or both. Further, the homogeneity in this cohort substantially reduces the confounding effect of socioeconomic status and education.⁴⁶ Education, in fact, was unrelated to incident AD, contrary to many⁴⁷⁻⁴⁹ but not all⁵⁰⁻⁵² previous prospective studies, possibly due to the high level of educational attainment in this cohort (88% with 16 years or more).

This study has several strengths, including a relatively long study period with an average of more than 5 evenly spaced observations per individual, follow-up participation exceeding 95%, use of uniform structured evaluations and widely accepted criteria applied by

board-certified neurologists to diagnose AD, and use of previously established composite measures of cognitive activity frequency and cognitive function. In addition, the clinical diagnosis of AD has been confirmed pathologically in more than 80% of cases evaluated to date.

Our study also has important limitations. The cohort is selected and differs from older persons in the US population in education, lifestyle, and perhaps other ways. It will be important, therefore, to replicate these findings in more diverse cohorts. Furthermore, our findings regarding the association of cognitive activity with reduced risk of AD only pertain to our composite measure of cognitive activity. More detailed studies are required to establish whether there is a differential effect of each of these activities on disease risk. Finally, the basis of the association of cognitive activity frequency with incident AD and rate of cognitive decline remains to be established. Disentangling the complex associations among cognitive activity, AD, and cognitive function is likely to require longer observational studies, clinical-pathological research, and evaluations of cognitive interventions.

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How will the truth be realized? What, in short, is the truth's cash-value in experimental terms? The moment pragmatism asks this question, it sees the answer: *True ideas* are those that we can assimilate, validate, corroborate, and verify. *False ideas* are those that we *cannot*. That is the practical difference it makes to us to have true ideas; that therefore is the meaning of truth, for it is all that truth is known as.

—William James (1842-1910)