ORIGINAL CONTRIBUTION

Leisure Activity and Cognitive Decline in Incident Alzheimer Disease

Elizabeth P. Helzner, PhD; Nikolaos Scarmeas, MD; Stephanie Cosentino, PhD;
Florence Portet, MD; Yaakov Stern, PhD

Background: High rates of leisure activity have been associated with reduced risk of Alzheimer disease (AD).

Objective: To determine whether prediagnosis leisure activity modifies the rate of cognitive decline in patients with AD.

Design: Inception cohort followed up longitudinally for a mean of 5.3 years (up to 13.9 years).

Setting: Urban community.

Participants: A total of 283 patients with incident AD (mean age, 79 years; 56.2% Hispanic and 31.1% African American).

Main Outcome Measures: Change in a composite cognitive score from diagnosis on and during the entire study follow-up.

Results: In multivariate-adjusted generalized estimating equation models of postdiagnosis change (n = 133), each leisure activity was associated with an additional yearly decline of 0.005 of a z-score unit in cognitive score ($P = .17$). In models expanded to include cognitive change during study follow-up, including evaluations before and after diagnosis (n = 283), each activity was associated with an additional yearly decline of 0.005 of a z-score unit in cognitive score ($P = .03$). The association was strongest for intellectual activities.

Conclusions: Greater participation in prediagnosis leisure activities, especially intellectual activities, was associated with faster cognitive decline, supporting the hypothesis that the disease course in AD may vary as a function of cognitive reserve.

Arch Neurol. 2007;64(12):1749-1754

Author Affiliations: Gertrude H. Sergievsky Center (Drs Helzner, Scarmeas, Cosentino, and Stern), Departments of Neurology (Drs Scarmeas and Stern) and Psychiatry (Dr Stern), and Taub Institute for Research in Alzheimer's Disease and the Aging Brain (Drs Scarmeas and Stern), Columbia University College of Physicians and Surgeons, New York, New York; and Memory Research Resource Center for Alzheimer's Disease, Neurology B Department, Institut National de la Sante et de la Recherche Medicale, Montpellier Hospital, Montpellier, France (Dr Portet).

H IGH RATES OF LEISURE AC- tivity have been associ- ated with reduced risk of Alzheimer disease (AD).[1-5] Along with pre- morbid IQ, educational level, and occu- pational attainment, leisure activity may contribute to cognitive reserve (CR).[6,7] Those with greater CR may tolerate a greater burden of Alzheimer neuropatho- logic conditions before clinical disease ex- pression; however, relatively advanced neuropathologic disease by the time of di- agnosis may result in faster disease pro- gression.[8,9] Proxies of higher CR, includ- ing higher educational level,[8,10,11] higher occupational attainment,[8,12] and higher premorbid reading activity,[13] have been as- sociated with faster cognitive decline in pa- tients with dementia, although some stud- ies[14,15] found no association.

The Washington Heights-Inwood Co- lumbia Aging Project (WHICAP) is a com- munity-based study of cognitive aging that began in 1989. An earlier WHICAP inves- tigation[4] found that high rates of leisure participation were associated with lower AD incidence. The current investigation assesses the influence of leisure on the rate of cognitive decline among those who de- veloped AD during study follow-up (ie, in- cident cases only). We hypothesized that higher prediagnosis leisure activity would be associated with faster cognitive de- cline, consistent with the hypothesis that leisure activity contributes to CR.

METHODS

SAMPLE

Participants in WHICAP were recruited in 2 similar cohorts. Recruitment began in 1992. The geographic study area was the 14 census tracts in Manhattan in New York, between (ap- proximately) 155th and 181st streets. Lists of all Medicare or Medicaid beneficiaries in this area were obtained from the Health Care Fi- nancing Administration (now called Centers for Medicare & Medicaid Services). Potential participants were then drawn by systematic ran- dom sampling into 1 of 6 strata formed based on ethnicity (Hispanic, non-Hispanic black, and non-Hispanic white) and age (65-74 and ≥75 years). A total of 2125 participants were inter-

viewed at baseline. A "refreshment" cohort of 2183 additional participants was formed in 1999 using generally similar methods. The main exceptions were as follows: new lists of beneficiaries were obtained but those drawn into the 1992 cohort were excluded, patients who reported being diagnosed as having dementia while arranging for the initial evaluation were excluded, and the study area was extended to the south and north to encompass all of Manhattan north of (approximately) 145th Street.

From the combined cohorts, 388 individuals developed AD during study follow-up. Of these, 318 had available follow-up assessments (15.0% of those without follow-up had not been seen for the next assessment wave). A total of 283 had prediagnosis leisure data and at least 2 cognitive assessments and were included in the analysis; of these, 133 had available postdiagnosis follow-up. Excluded patients with AD were older than the analysis sample (*P*=.04) but did not significantly differ by sex, race, *APOE* ε4 status, educational level, leisure participation, or baseline cognitive score. The study was approved by the Columbia University institutional review board, and written informed consent was obtained from all participants.

ASSESSMENT OF INCIDENT AD

Diagnoses of AD were based on standardized, physician-administered physical and neurologic examinations along with a standardized neuropsychological battery. All assessments were administered at baseline and at subsequent follow-ups (roughly every 18 months). Assessments were conducted in English or Spanish based on participant preference. All available ancillary information (medical records, imaging studies, and evidence of social or occupational function deficits) was considered. Leisure information was not used in diagnosis.

Dementia diagnoses were made at consensus conferences attended by neurologists and neuropsychologists based on *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) criteria. Probable or possible AD was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association.

OUTCOME MEASURES

The primary outcome was rate of change in a composite measure of cognition. A complete neuropsychological battery[16] was administered, with tests that assessed 5 cognitive domains: (1) memory: total and delayed recall of the Selective Reminding Test[17] and the recognition component of the multiple-choice version of the Benton Visual Retention Test[18]; (2) abstract reasoning: Wechsler Adult Intelligence Scale Revised similarities subtest[19] and the identities and oddities subtest of the Dementia Rating Scale[20]; (3) visual-spatial: 5 items from the Rosen Drawing Test[21] and the matching component of the multiple-choice version of the Benton Visual Retention Test[18]; (4) language: 15-item Boston Naming Test,[22] the 8 high-probability items from the repetition subtest of the Boston Diagnostic Aphasia Examination,[22] and the first 6 items of the Boston Diagnostic Aphasia Examination comprehension subtest; and (5) executive speed: average scores for phonemic fluency assessed by the Controlled Oral Word Association Test and category fluency (animals, food, and clothing) mean scores.[23]

The composite measure was derived as follows: the 12 raw scores were transformed into *z* scores based on means and standard deviations for each test calculated from baseline scores of 272 control subjects who were matched according to age, education level, and ethnicity to identify patients with incident AD. Individual test *z* scores for participants with dementia were av-

eraged to create a *z* score for each cognitive domain. If fewer than half of the test *z* scores were missing for a given domain, the domain score was calculated with the available data. If more than half of the tests were missing, the domain score was considered missing and was excluded. The composite score was the average of the 5 domain scores, with missing data treated in the manner previously described.

PREDICTOR VARIABLES

The primary predictor variable was self-reported leisure activity. Although leisure was measured at multiple visits, the first available assessment was used for 2 reasons: (1) to increase response validity, since participants did not have dementia at this visit, and (2) to better approximate long-standing leisure habits (to better approximate CR). Participation in the previous month in 13 activities was considered in 4 categories according to previous work[4]: (1) intellectual: reading magazines, newspapers, or books; going to classes; and playing cards, games, or bingo; (2) social: doing unpaid volunteer work; going to a club or center; going to movies, restaurants, or sporting events; attending church, synagogue, or temple; visiting friends or relatives; and being visited by friends or relatives; (3) physical: physical conditioning and walking for pleasure or excursion; and (4) other: knitting, music, or other hobby and watching television or listening to the radio. Participation in each activity was scored 1 point and summed to derive the total leisure activity score (range, 0-13). High vs low rates of leisure participation were based on a median split of 6 activities.[4]

We also considered factors that might influence cognitive decline or leisure participation. Baseline medical comorbidity was assessed with a modified[24] Charlson Comorbidity Index.[25] Myocardial infarction, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal disease, mild liver disease, and diabetes mellitus were weighted 1; chronic renal disease and systemic malignancy were weighted 2. History of stroke was considered separately. The *APOE* genotype was determined using established methods[26] and categorized based on the presence of at least 1 ε4 allele. We also considered ethnicity (non-Hispanic white, non-Hispanic black, and Hispanic), sex, education level, baseline cognitive performance, and study cohort.

STATISTICAL ANALYSES

Baseline characteristics by leisure category (low or high) were compared using χ^2 or *t* tests. Generalized estimating equations were used to examine influence of leisure on rates of postdiagnosis cognitive change. By treating each patient's repeated measures as a cluster, the generalized estimating equations account for the probable correlation of characteristics measured in the same individual over time. In the initial model, the dependent variable was the composite cognitive score. Predictor variables were total leisure score, time (years from diagnosis), and a leisure × time interaction. A significant leisure effect would suggest a difference in cognitive performance at diagnosis associated with each prediagnosis leisure activity. A significant time effect would suggest a change in cognitive scores over time (regardless of leisure score). A significant interaction term would suggest differential rates of cognitive change as a function of leisure.

Subsequently, multivariate-adjusted models were constructed. Since low leisure activity measured closer to diagnosis could reflect early dementia, we controlled for time between the leisure assessment and dementia diagnosis (leisure-to-diagnosis time) in all models. Models also included baseline cognitive score, ethnicity, educational level, sex, study co-

Characteristics	Entire Sample (N=283)[a]	Low Leisure Participation (n=143)[a,b]	High Leisure Participation (n=140)[a,c]	P Value (Difference)
Age, y				
At baseline visit	78.7±6.6	79.0±6.7	78.5±6.5	.39
At dementia diagnosis	83.1±6.5	83.4±7.0	82.9±5.9	.47
Education level, y	7.0±4.5	6.8±4.5	7.1±4.6	.76
Male	83 (29.3)	41 (28.7)	42 (30.0)	.81
Ethnicity				
White	34 (11.1)	19 (13.3)	14 (10.0)	.58
African American	88 (31.1)	40 (28.0)	58 (34.3)	
Hispanic	159 (56.2)	82 (57.3)	77 (55.0)	
Other	3 (1.1)	2 (1.4)	1 (0.7)	
Baseline cognitive score	−0.60±0.62	−0.69±0.61	−0.50±0.63	.01
Presence of at least 1 APOE ε4 allele	81 (28.6)	46 (34.8)	35 (28.0)	.24
History of stroke	64 (22.6)	40 (28.0)	24 (17.1)	.03
Baseline Charlson comorbidity index score	2.6±1.5	2.9±1.6	2.3±1.4	.002
Follow-up time, y	5.3±3.1	5.4±3.0	5.2±3.2	.50
Time between leisure assessment and AD incidence, y	4.1±2.8	4.2±2.8	4.2±2.8	.87

Abbreviation: AD, Alzheimer disease.
[a] Data are presented as mean±SD and number (percentage).
[b] Participation in 6 or fewer leisure activities at baseline.
[c] Participation in more than 6 leisure activities at baseline.

hort, comorbidity index, and stroke history. All covariates were simultaneously introduced into models. A separate model was built for each leisure category (total leisure, intellectual, social, physical, and other activities).

In supplementary analyses, we examined cognitive decline during the entire study follow-up (before and after diagnosis). This was done to more fully capture the natural course of the disease, since AD-associated neuropathologic conditions and subtle cognitive decline are present many years before diagnosis.[27,28] Also, in this sample, rates of cognitive decline were similar before and after AD diagnosis.[28] In exploratory analyses, we examined leisure-associated decline within APOE ε4 strata.

<h2 style="text-align:center">RESULTS</h2>

CHARACTERISTICS OF THE SAMPLE

At diagnosis, most participants (89%) had a clinical dementia rating of 1.0 (mild).[29] Leisure participation did not vary by education level, sex, ethnicity, or age (at baseline or diagnosis). Higher leisure activity was associated with higher baseline cognition, fewer medical comorbidities, and lower stroke prevalence (**Table 1**). Treating leisure as a continuous variable (number of activities), leisure activity was positively correlated with years of education ($r=0.004$; $P=.95$), and intellectual leisure activity examined separately was positively correlated with years of education ($r=0.07$; $P=.26$), although these findings did not reach statistical significance.

The mean±SD follow-up time between baseline and last cognitive assessments was 5.3±3.1 years (range, 1.0-13.9 years), with a mean±SD of 3.6±1.5 follow-up assessments (range, 2-5). The mean±SD time between leisure assessment and AD diagnosis was 4.1±2.8 years (range, 1.0-13.1 years). Those with postdiagnosis follow-up (n=133) had a mean±SD postdiagnosis follow-up of 3.3±2.1 years

(range, 1.1-9.8 years) and a mean±SD of 2.4±0.8 postdiagnosis assessments (range, 1-5).

COGNITIVE DECLINE OVER TIME

As expected in this sample with dementia, the composite cognitive score declined during study follow-up. In a generalized estimating equations model, the β associated with the composite cognitive score was −.09 ($P<.001$), indicating a 9% decline per year. Rates of decline were similar before ($β=−.08$; $P<.001$) and after ($β=−.09$; $P<.001$) AD onset. Quadratic terms for time were added to these models to test whether cognitive change was nonlinear. These terms were nonsignificant and thus were not included in the final models.

LEISURE ACTIVITY AND COGNITIVE DECLINE

The primary models examined cognitive change after diagnosis and were limited to 133 participants. Higher total leisure scores were associated with faster cognitive decline, although this effect did not reach statistical significance ($β=−.005$; $P=.17$). Leisure categories (physical, social, intellectual, and other) were subsequently examined separately. After multivariate adjustment, no statistically significant effects by leisure category were seen (**Table 2**).

SUPPLEMENTARY ANALYSES

Models that examined cognitive decline during the entire study follow-up (before and after diagnosis) included 283 participants. In this much larger sample, each leisure activity was associated with an additional yearly decline of 0.005 of a z-score unit ($P=.03$) after multivariate adjustment. **Figure 1** illustrates predicted de-

Table 2. Separate Multivariate-Adjusted Generalized Estimating Equation Models That Measured Leisure-Associated Decline in Cognitive Function[a]

Variable	Change From Diagnosis (n = 133)		Change From Study Baseline (n = 283)	
	β	P Value	β	P Value
Total leisure score	−.020	.24	.002	.72
Time total leisure score	−.005	.17	**−.006**	**.02**
Physical leisure	.027	.60	.002	.92
Time physical leisure	.004	.72	−.010	.19
Social leisure	−.041	.12	.004	.69
Time social leisure	−.011	.10	−.006	.09
Intellectual leisure	−.004	.92	.019	.40
Time intellectual leisure	−.007	.37	**−.029**	**.001**
Other leisure	.103	.28	−.028	.40
Time other leisure	.001	.95	.013	.33

[a] All models included the following covariates entered simultaneously: age, sex, ethnicity, education level, baseline Charlson Comorbidity Index score, stroke history, study cohort, baseline cognitive function, and time between the leisure assessment and the diagnosis visit. Statistically significant (P<.05) coefficients are set in boldface type.
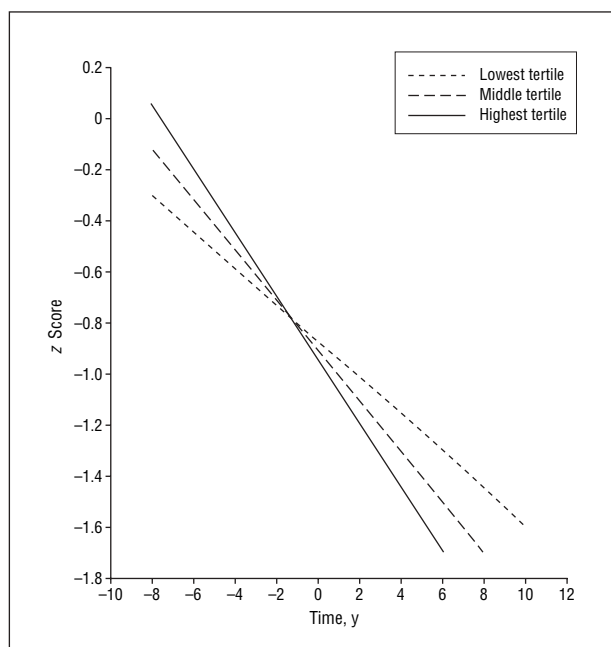

Figure 1. Predicted decline in composite cognitive score based on generalized estimating equations by tertile of baseline leisure activity. Time 0 indicates diagnosis visit. Negative times reflect prediagnosis visits.

cline in composite cognitive score based on generalized estimating equations by tertile of baseline leisure activity. In category-specific models, only intellectual activity was associated with faster decline, with an additional decline of 0.03 of a z-score unit per activity per year (P<.001) (Table 2).

EXPLORATORY ANALYSES

APOE ε4–Stratified Models

Since *APOE* ε4 has been associated with differential rates of cognitive decline, we repeated models after stratifying by ε4 status. Because of incomplete *APOE* data, we were underpowered to test this association using only postdiagnosis cognitive change; thus, these models measured change during the entire study. Higher total leisure activity was associated with faster cognitive decline among non-ε4 carriers only (β=−.007, P=.04; among ε4 carriers: β=.003, P=.46; fully adjusted models).

Models of Leisure-Associated Change in Specific Cognitive Domains

We performed the analysis again with the total leisure score as the primary predictor, examining change in specific cognitive domains. In models of postdiagnosis change, differential rates of change were seen for the executive speed domain (β=−.10; P=.03) but not in other domains (memory: β=−.004, P=.47; visuospatial: β=−.003, P=.58; abstract reasoning: β=−.001, P=.82; language: β=−.005, P=.30). In models of cognition from baseline on, differential rates of change were seen in the memory (β=−.009; P=.05) and executive speed (β=−.009; P=.02) domains but not the others (visuospatial: β=−.004, P=.42; abstract reasoning: β=−.001, P=.73; language: β=−.007; P=.27).

COMMENT

To our knowledge, this study is the first to examine the influence of premorbid leisure activity on cognitive decline among incident AD cases. In models of postdiagnosis cognitive change, leisure categories were associated with faster cognitive decline, although the effect did not reach statistical significance. Supplementary analyses that measured cognitive decline during the entire study follow-up, potentially capturing earlier disease stages and more than doubling the sample size, revealed that higher total leisure and intellectual activity (but not social or physical activity) was associated with significantly faster cognitive decline, even after multivariate adjustment.

We hypothesized that leisure activity serves as a proxy of CR. People with high CR may have more efficient neu-
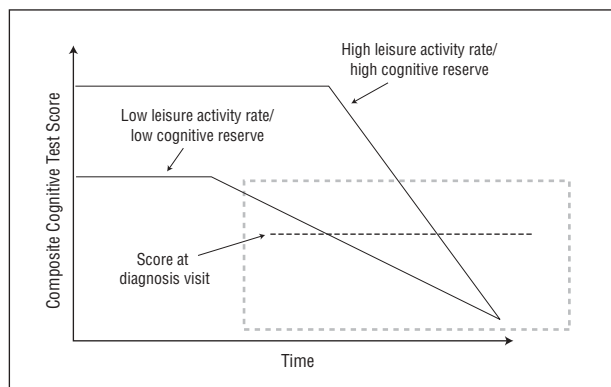
Figure 2. Theoretical model to explain more rapid cognitive decline in patients with higher leisure activity rates. People with high rates of leisure activity are protected in that decline starts later, as indicated by previous studies. However, once decline starts, it follows a more precipitous course in the high leisure activity rate group. The highlighted area corresponds to the period examined in this study. Note that decline has begun even before diagnosis.

ral networks or may use alternate networks more effectively after neurologic insult. These people theoretically compensate better for AD-associated neuropathologic conditions, allowing for a longer period of normal function before diagnosis. Thus, those with higher CR may have lower or delayed AD incidence. However, since neuropathologic conditions are relatively advanced by diagnosis,[24,30-32] they may have a faster subsequent disease course.[6]

Support for this theory comes from studies that demonstrated faster cognitive decline among patients with AD with higher education levels[8,10,24] and higher premorbid reading activity.[13] Furthermore, imaging studies suggest that CR may modulate the relationship between neuropathologic disease and clinical manifestations. Adjusting for clinical severity, more highly educated patients with AD tolerated greater cerebral blood flow deficits (an indirect measure of AD),[30] and patients with AD with higher occupational attainment and higher premorbid intelligence demonstrated lower cerebral metabolism.[31,32] In our earlier positron emission tomographic study of patients with AD, those with a high leisure activity rate tolerated greater cerebral blood flow deficits (suggesting greater neuropathologic disease), even adjusted for disease severity, educational level, and IQ.[24] Our current findings are consistent with imaging results, suggesting that higher premorbid leisure activity is linked to more advanced neuropathologic disease, resulting in faster subsequent progression. Our findings also mirror the recent results regarding educational level from this cohort,[24] despite the lack of correlation between leisure activity and educational attainment, suggesting that leisure activity may represent an aspect of CR distinct from education level. A theoretical model of leisure as a proxy of CR is presented in **Figure 2**.

We found no association between physical activity and cognitive decline in patients with AD. The mental stimulation associated with intellectual and social activities may influence CR differently than physical activity. Alternatively, our negative findings with physical activity may be due to our admittedly limited physical activity assessment.

Exploratory models stratified by *APOE* ε4 status revealed that leisure-associated cognitive decline during the entire study follow-up was more pronounced among non-ε4 carriers, suggesting that the effect of *APOE* ε4 may override any contributing effect of leisure on cognitive decline among carriers.

A major strength of this study is that the sample was limited to cases of incident AD, allowing us to capture more of the disease course, including the earlier stages. Other strengths include the high quality of our diagnostic procedure and our use of multiple cognitive assessments to provide more accurate slope calculations. Finally, our ethnically diverse, community-based sample increases generalizability of our findings.

We acknowledge several limitations. Although we used the earliest available leisure measurement, this was on average only 4 years before diagnosis. If early dementia reduced leisure activity, this might work against our findings. We attempted to account for this by controlling for time between the leisure assessment and dementia incidence for each participant. In future investigations, it would be better to assess leisure earlier in life. Unlike others,[5] we did not measure frequency and intensity of activities, possibly reducing the sensitivity of our leisure assessment. Finally, we cannot exclude the possibility that leisure acts as a surrogate for some other factor not included in our models that is truly associated with faster cognitive decline. Our results add to the growing body of evidence that disease course in AD may vary as a function of CR.

REFERENCES

1. Fabrigoule C, Letenneur L, Dartigues JF, et al. Social and leisure activities and risk of dementia: a prospective longitudinal study. *J Am Geriatr Soc.* 1995; 43(5):485-490.
2. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal

study from the Kungsholmen Project. *Am J Epidemiol.* 2002;155(12):1081-1087.

3. Wilson RS, Bennett DA, Bienias JL, et al. Cognitive activity and incident AD in a population-based sample of older persons. *Neurology.* 2002;59(12):1910-1914.

4. Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's Disease. *Neurology.* 2001;57(12):2236-2242.

5. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med.* 2003;348(25):2508-2516.

6. Stern Y. What is cognitive reserve? theory and research application of the reserve concept. *J Int Neuropsychol Soc.* 2002;8(3):448-460.

7. Scarmeas N, Stern Y. Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep.* 2004;4(5):374-380.

8. Stern Y, Albert S, Tang MX, Tsai WY. Rate of memory decline in AD is related to education and occupation: cognitive reserve? *Neurology.* 1999;53(9):1942-1947.

9. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev.* 2004;3(4):369-382.

10. Teri L, McCurry SM, Edland SD, Kukull WA, Larson EB. Cognitive decline in Alzheimer's disease: a longitudinal investigation of risk factors for accelerated decline. *J Gerontol A Biol Sci Med Sci.* 1995;50A:M49-M55.

11. Rasmusson DX, Carson KA, Brookmeyer R, Kawas C, Brandt J. Predicting rate of cognitive decline in probable Alzheimer's disease. *Brain Cogn.* 1996;31(2):133-147.

12. Wilson RS, Li Y, Aggarwal NT, et al. Education and the course of cognitive decline in Alzheimer disease. *Neurology.* 2004;63(7):1198-1202.

13. Wilson RS, Bennett DA, Gilley DW, Beckett LA, Barnes LL, Evans DA. Premorbid reading activity and patterns of cognitive decline in Alzheimer disease. *Arch Neurol.* 2000;57(12):1718-1723.

14. Haxby JV, Raffaele K, Gillette J, Schapiro MB, Rapoport SI. Individual trajectories of cognitive decline in patients with dementia of the Alzheimer type. *J Clin Exp Neuropsychol.* 1992;14(4):575-592.

15. Bowler JV, Munoz DG, Merskey H, Hachinski V. Factors affecting the age of onset and rate of progression of Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 1998;65(2):184-190.

16. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogenous population: development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. *Arch Neurol.* 1992;49(5):453-460.

17. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology.* 1974;24(11):1019-1025.

18. Benton A. *The Visual Retention Test.* New York, NY: The Psychological Corp; 1955.

19. Wechsler D. *Wechsler Adult Intelligence Scale Revised.* New York, NY: The Psychological Corp; 1981.

20. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, ed. *Geriatric Psychiatry.* New York, NY: Grune & Stratton; 1976:77-121.

21. Rosen WG. *The Rosen Drawing Test.* Bronx, NY: Veterans Administration Medical Center; 1981.

22. Goodglass H. *The Assessment of Aphasia and Related Disorders.* 2nd ed. Philadelphia, PA: Lea & Febiger; 1983.

23. Benton AL. *Manual for the Multilingual Aphasia Examination.* 3rd ed. Iowa City, IA: AJA Associates Inc; 1994.

24. Scarmeas N, Albert M, Brandt J, et al. Motor signs predict poor outcomes in Alzheimer disease. *Neurology.* 2005;64(10):1696-1703.

25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.

26. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res.* 1990;31(3):545-548.

27. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort. *Arch Neurol.* 2000;57(6):808-813.

28. Scarmeas N, Albert SM, Manly JJ, Stern Y. Education and rates of cognitive decline in incident Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2006;77(3):308-316.

29. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993;43(11):2412-2414.

30. Stern Y, Alexander GE, Prohovnik I, Mayeux R. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. *Ann Neurol.* 1992;32(3):371-375.

31. Stern Y, Alexander GE, Prohovnik I, et al. Relationship between lifetime occupation and parietal flow: implications for a reserve against Alzheimer's disease pathology. *Neurology.* 1995;45(1):55-60.

32. Alexander GE, Furey ML, Grady CL, et al. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. *Am J Psychiatry.* 1997;154(2):165-172.

Announcement

Topic Collections. *Archives* offers collections of articles in specific topic areas to make it easier for physicians to find the most recent publications in a field. These are available by subspecialty, study type, disease, or problem. In addition, you can sign up to receive a Collection E-Mail Alert when new articles on specific topics are published. Go to http://archneur.ama-assn.org /collections to see these collections of articles.