Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia

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ABSTRACT

Objective: To examine the relation of performance on brief cognitive tests to development of clinically diagnosed Alzheimer disease (AD) dementia over the following 18 years in a sample of African Americans and European Americans.

Methods: A composite cognitive test score based on tests of episodic memory, executive function, and global cognition was constructed in a prospective population-based sample of 2,125 participants (55% African American and 61% female) aged 65 years and older residing in 4 Chicago neighborhoods. Time before AD dementia diagnosis was categorized into 6 groups corresponding to data collection periods: 0.1–0.9, 1.0–3.9, 4.0–6.9, 7.0–9.9, 10.0–12.9, and 13.0–17.9 years.

Results: Of 2,125 participants without clinical AD dementia, 442 (21%) developed clinical AD dementia over 18 years of follow-up. Lower composite cognitive test scores were associated with the development of AD dementia over the duration of the study. The magnitude of association between composite cognitive test score and development of AD dementia increased from an odds ratio of 3.39 (95% confidence interval 1.72, 6.67; $p < 0.001$) at 13.0–17.9 years to 9.84 (95% confidence interval 7.41, 13.06; $p < 0.001$) at 0.1–0.9 years, per SD increment. These associations were consistently larger among European Americans than among African Americans. Performance on individual cognitive tests of episodic memory, executive function, and global cognition also significantly predicted the development of AD dementia, with associations exhibiting a similar trend over 18 years.

Conclusions: Our findings suggest that cognitive impairment may manifest in the preclinical phase of AD dementia substantially earlier than previously established. *Neurology*® 2015;85:898–904

GLOSSARY

AD = Alzheimer disease; CI = confidence interval; OR = odds ratio.

Because of the lack of effective treatments for Alzheimer disease (AD) dementia, early preventive efforts may be more effective in slowing preclinical manifestation of AD dementia.^{1,2} As a consequence, the long duration of preclinical AD dementia has been a major point of emphasis.^{3–5} Although our direct knowledge of the preclinical sequences and interrelations of cognitive and pathologic events are limited, pathologic events are generally thought to begin much earlier than clinical ones.^{6,7} Imaging-based studies suggest an initial deficiency in limbic regions of the brain affecting episodic memory in the early stages of the disease,^{8,9} that progresses to the cortical regions of the brain followed by other cognitive symptoms, and an AD dementia syndrome is noticed.^{10–12} Much of this knowledge is from investigations confined to clinical settings rather than from the general population.

Cognitive test performance predicts development of subsequent AD dementia in European American populations.^{13–17} Several prospective studies suggest detectable cognitive deficits up to 10 years before clinical diagnosis of AD dementia,^{18–24} and 2 studies suggest these deficits may be detected as long as 10 to 12 years before diagnosis.^{25,26} However, little information is available

Supplemental data
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about earlier deficits or about the preclinical phase of AD dementia in minority groups. We examined the relation of cognitive test performance to subsequent development of clinical AD dementia over intervals ranging from 1 to 18 years among older African Americans and European Americans. Cognition was assessed using a battery of 4 brief cognitive tests. The diagnosis of AD dementia was based on a uniform evaluation by clinicians blinded to previously collected data.

METHODS Study design and participants. The Chicago Health and Aging Project is a longitudinal, population-based study of AD dementia and other health conditions among adults aged 65 years and older conducted from 1993 to 2012, which enrolled 78.7% of all residents older than 65 years from a geographically defined biracial community of African Americans and European Americans. Residents who reached 65 years of age in subsequent years were also enrolled in successive age cohorts. These participants had less follow-up than those enrolled at the beginning of the study. The Chicago Health and Aging Project study design has been described in detail previously.^{27,28} Cognitive tests were administered during population interviews that were conducted in participants' homes in approximately 3-year cycles for up to 6 cycles over 18 years.

A detailed flowchart for selection of the clinical sample from the population sample is shown in figure e-1 on the *Neurology*[®] Web site at Neurology.org. Participants with follow-up had higher cognitive function scores ($p < 0.0001$) than participants lost to follow-up (0.389 vs 0.203) and deceased (0.389 vs -0.514). Of the 10,801 participants in the population sample, 3,182 were selected for clinical evaluations, of which 1,033 were excluded for prevalent AD dementia, and 24 with non-AD dementia were also excluded, resulting in a sample size of 2,125.

Standard protocol approvals, registrations, and participant consents. The Rush University Medical Center institutional review board approved this study. All participants provided written informed consent.

Cognitive function assessment. Cognitive function was evaluated using a battery of 4 tests including 2 tests of episodic memory (Immediate and Delayed Recall of the East Boston Story),^{29,30} a test of executive function (Symbol Digits Modalities Test),³¹ and a test of general orientation and global cognition (Mini-Mental State Examination).³² In a factor analysis, these tests loaded on a single factor accounting for about 75% of the variance.³³ Hence, a composite cognitive test score based on all 4 tests by averaging the 4 tests together after centering and scaling each to their baseline mean and SD was constructed. A participant whose composite performance matches the average participant at baseline has a composite score of 0, whereas positive and negative scores were indicators of better and poorer cognitive performances, respectively. Cognitive tests of episodic memory were based on the average of the 2 recall untransformed test scores (range: 0–12), executive function was based on untransformed Symbol Digits Modalities Test score (range: 0–75), and global cognition was based on untransformed Mini-Mental State Examination test score (range: 0–30).

AD dementia diagnosis. Individuals sampled for clinical assessment underwent a uniform clinical evaluation that included

a structured medical history, neurologic examination, and a battery of 19 cognitive function tests. On the basis of this evaluation, a board-certified neurologist, who was unaware of previously collected data, diagnosed dementia and AD according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria,³⁴ as previously described.³⁰ These require a history of cognitive decline and evidence of impairment in 2 or more cognitive domains, one of which must be memory, for a diagnosis of AD dementia.

Covariates. All of our regression models adjusted for age (measured in years and centered at 75), sex (males or females), race (when using entire sample), and education (measured in number of years of schooling completed centered at 12). Because years of education is not commensurate between older African Americans and European Americans,³⁵ we replaced educational attainment with 2 measures—early-life cognitive activity and early-life household socioeconomic and community socioeconomic level. Early-life cognitive activity was based on 3 questions: “How often did someone in your home read to you as a child?” “How often did someone in your home tell you stories when you were a child?” and “How often did someone in your home play games with you when you were a child?” Participants rated their frequency of participation in each activity on a 5-point scale: 5 = every day or almost every day; 4 = several times a week; 3 = several times a month; 2 = several times a year; and 1 = once a year or less. These ratings were averaged to yield a composite measure of cognitive activity, which ranged from 1 to 5, with higher scores indicating more frequent early-life cognitive activity. Early-life household socioeconomic and community socioeconomic level was based on a standardized composite measure of parental education and socioeconomic features of the birth county (e.g., literacy rate and birth county expenditure on education).

Statistical analyses. Descriptive analysis was performed using means and SDs for continuous measures, and percentages for categorical measures. Approximately 3% of participants had at least one missing cognitive function test but still had a clinical diagnosis of AD dementia. These participants with missing cognitive data were removed from analysis for missing individual cognitive function test, but were used in the composite cognitive function test that was created with available cognitive function tests. Our initial descriptive analysis was stratified by race; and later descriptive analysis by development of clinical AD dementia status. We also made descriptive comparisons using a 2-sample independent t test for continuous measures, and χ^2 test statistic for categorical measures. Given that our cognitive test scores from population interviews were collected over 6 triennial cycles with diagnosis of clinical AD dementia assessed less than 1 year after their last cognitive assessment, we created 6 classifications to denote time before development of clinical AD dementia: 0.1–0.9, 1.0–3.9, 4.0–6.9, 7.0–9.9, 10.0–12.9, and 13.0–17.9 years. The main objective of this investigation was to examine the association of cognitive function test levels with future development of AD dementia. Consistent with this objective, we used a logistic regression model with cognitive test scores to predict future development of clinical AD dementia at each time interval after adjusting for demographic covariates previously described.³⁶ Our primary set of models used a composite cognitive test score to predict future development of clinical AD dementia in the entire sample, as well as in African Americans and European Americans, separately. In a separate analysis, we also included race interactions to examine the possible differences in the association of composite cognitive function with clinical

Table 1 Descriptive analysis of demographic characteristics and cognitive test scores at the baseline assessment in 2,125 African Americans and European Americans

	Overall	African Americans	European Americans
	N = 2,125	N = 1,158	N = 967
Age, y	73.1 (5.9)	71.7 (5.1)	74.7 (6.3)
Education, y	13.0 (3.4)	11.9 (3.2)	14.2 (3.2)
Composite cognition	0.493 (0.521)	0.346 (0.543)	0.668 (0.434)
Episodic memory	9.2 (2.1)	8.9 (2.2)	9.5 (1.9)
Executive function	33.8 (12.3)	29.4 (12.1)	39.0 (10.2)
Global cognition	27.8 (2.3)	27.2 (2.6)	28.5 (1.7)
Females, n (%)	1,325 (62)	731 (63)	594 (61)
Income, n (%)			
\$0–\$14,999	613 (29)	457 (40)	156 (16)
\$15,000–\$29,999	763 (36)	460 (40)	303 (32)
Above \$30,000	731 (35)	237 (20)	494 (52)

Data represent mean (SD) unless otherwise indicated.

development of AD dementia between African Americans and European Americans. We also performed a sensitivity analysis by replacing years of formal education with early-life cognitive activity and early-life household socioeconomic and community socioeconomic level. Our secondary set of models used episodic memory, executive function, and global cognition test scores to predict future development of clinical AD dementia in the entire sample. All models were fitted in SAS software.³⁷

RESULTS Of the 2,125 older adults, 442 (21%) developed AD dementia during the follow-up period with a higher cumulative incidence proportion among African Americans (23%) than among European Americans (17%). The average age at diagnosis of clinical AD dementia was 83.6 (SD = 5.9) years.

Participants with clinical evaluations had significantly higher baseline cognitive function scores than participants selected but deceased (0.493 vs 0.243; $p < 0.0001$), and similar scores to participants who

were selected but did not participate (0.493 vs 0.477; $p = 0.58$). Also, participants with clinical evaluations had significantly higher cognitive function test scores in the population interview before selection than participants selected but deceased (-0.027 vs -0.464 ; $p < 0.0001$) and those who were selected but did not participate (-0.027 vs -0.175 ; $p < 0.0001$).

Participants at initial assessment. Table 1 shows the characteristics of African American and European American participants at their baseline cognitive assessment. African Americans were about 3 years younger and had about 2 fewer years of education than European Americans. The 2 groups differed substantially by income as well, with approximately 80% of African Americans (vs 48% of European Americans) having annual household incomes of less than \$30,000. African American participants also had lower composite cognitive test scores and lower scores on tests of episodic memory, executive function, and global cognition.

Diagnosis of clinical AD dementia over time. During the 0.1- to 0.9-year interval between cognitive assessment and diagnostic testing, about 22% of African Americans and 17% of European Americans developed clinical AD dementia after an average of 0.5 (SD = 0.21) years (table 2). The second time interval, 1.0–3.9 years, corresponds to the cognitive assessment 2 data-cycles, 4.0–6.9 to 3 data-cycles, 7.0–9.9 to 4 data-cycles, 10.0–12.9 to 5 data-cycles, and 13.0–17.9 to 6 data-cycles before diagnosis of AD dementia. The proportion diagnosed with clinical AD dementia was mostly steady among African Americans, in the low to mid 20% over the duration of the study. European Americans, however, showed a continual increase in proportion developing AD dementia, over the duration of the study, from 10% to 17%.

Composite cognitive test score and development of AD dementia. Table 3 shows average composite cognitive

Table 2 Time to diagnosis of clinical AD dementia and number of participants who developed AD dementia during an 18-year period after initial cognitive testing

Years before AD dementia diagnosis	African Americans			European Americans		
	No.	Time to diagnosis ^a	AD dementia, n (%)	No.	Time to diagnosis ^a	AD dementia, n (%)
0.1–0.9	864	0.5 (0.22)	186 (22)	673	0.5 (0.22)	114 (17)
1.0–3.9	948	2.8 (0.98)	242 (26)	838	2.8 (0.98)	148 (18)
4.0–6.9	901	5.4 (1.04)	214 (24)	745	5.5 (1.01)	121 (16)
7.0–9.9	665	8.4 (1.05)	151 (23)	432	8.6 (1.05)	67 (16)
10.0–12.9	281	11.3 (1.05)	72 (26)	225	11.3 (1.13)	35 (16)
13.0–17.9	265	14.7 (1.45)	61 (23)	164	14.4 (1.31)	17 (10)

Abbreviation: AD = Alzheimer disease.

^aMean (SD) time in years between cognitive test scores and clinical evaluation for diagnosis of AD dementia.

Table 3 Differences in composite cognitive test scores in participants free of AD dementia and those who developed AD dementia over an 18-year period

Years before diagnosis	Time to diagnosis	Free of AD dementia	Developed AD dementia	p Value ^a
0.1–0.9	0.5 (0.22)	0.301 (0.532)	–0.645 (0.725)	<0.001
1.0–3.9	2.8 (0.98)	0.524 (0.485)	–0.138 (0.659)	<0.001
4.0–6.9	5.4 (1.02)	0.569 (0.453)	0.186 (0.484)	<0.001
7.0–9.9	8.5 (1.05)	0.523 (0.472)	0.193 (0.479)	<0.001
10.0–12.9	11.3 (1.08)	0.534 (0.460)	0.245 (0.451)	<0.001
13.0–17.9	14.6 (1.40)	0.579 (0.440)	0.258 (0.501)	<0.001

Abbreviation: AD = Alzheimer disease.

Data represent mean (SD).

^aBased on 2-sided t tests for 2 independent samples.

test scores of those who were free of AD dementia and those who developed clinical AD dementia. In each interval, average cognitive test scores among those who developed AD dementia were significantly lower than among those who remained free of AD dementia. During 0.1–0.9 years before development of AD dementia, the composite cognitive test score was 0.946 units (SD units) lower among those who developed AD dementia compared with those who remained free of AD dementia ($p < 0.001$). Despite diminishing differences further back in time before diagnosis, the difference of 0.321 units observed during 13.0–17.9 years was substantial and remained significant ($p < 0.001$).

Using logistic regression models adjusted for age, sex, and education, our composite cognitive test scores predicted development of clinical AD dementia over the duration of the 18-year study (table 4). The estimated odds ratios (ORs) diminished with increasing time before AD dementia assessment but remained significant even at the time farthest from

Table 4 Odds ratios for composite cognitive test score predicting the development of clinical Alzheimer disease dementia among African and European Americans over an 18-year period

Years before diagnosis	Overall ^a	African Americans ^b	European Americans ^b
0.1–0.9	9.84 (7.41, 13.06) ^c	8.71 (6.04, 12.54) ^c	12.20 (7.70, 19.34) ^c
1.0–3.9	7.57 (5.76, 9.96) ^c	5.77 (4.15, 8.02) ^c	13.61 (8.29, 22.35) ^c
4.0–6.9	6.80 (4.91, 9.39) ^c	5.01 (3.39, 7.40) ^c	13.54 (7.40, 24.75) ^c
7.0–9.9	3.54 (2.45, 5.12) ^c	3.01 (1.98, 4.58) ^c	7.10 (3.20, 15.75) ^c
10.0–12.9	3.96 (2.24, 7.00) ^c	3.40 (1.74, 6.64) ^c	8.60 (2.62, 28.25) ^c
13.0–17.9	3.39 (1.72, 6.67) ^c	2.93 (1.35, 6.38) ^d	5.62 (1.14, 27.7) ^e

Data represent odds ratio (95% confidence interval).

^aAdjusted for age, sex, race, and education.

^bAdjusted for age, sex, and education.

^c $p < 0.001$.

^d $p < 0.01$.

^e $p < 0.05$.

AD dementia assessment. In the 0.1–0.9 years before diagnostic assessment, cognitive test score was associated with OR of 9.84 (per SD increment in score; 95% confidence interval [CI] 7.41, 13.06; $p < 0.001$) for developing clinical AD dementia. The association of cognitive function tests with incident AD dementia decreased with increasing lapse in time between cognitive assessments, but it was still present for the earliest cognitive function tests administered 13.0–17.9 years before development of clinical AD dementia ($p < 0.001$).

Composite cognitive test scores also predicted the development of clinical AD dementia among African Americans and European Americans over the entire duration of the 18-year study, even though the ORs were larger among European Americans than among African Americans (table 4). Among African Americans and European Americans, the association of composite cognitive test score with development of AD dementia decreased from 0.1–0.9 years to 13.0–17.9 years before diagnostic assessment. The OR estimates were about 1.5- to 2.5-fold higher in European Americans than in African Americans with the largest difference at 4.0–6.9 years before development of AD dementia ($p = 0.008$). The association of cognitive score with AD dementia risk was also significantly larger among European Americans at 1.0–3.9 years ($p = 0.038$).

Performance in individual cognitive domains and development of AD dementia. Scores on tests of episodic memory, executive function, and global cognition predicted development of clinical AD dementia in this population over the 18-year period (table 5).

Episodic memory predicted development of clinical AD dementia over the 18-year study with OR declining from 0.1–0.9 years to 13.0–17.9 years. The ORs for executive function and global cognition showed a similar pattern of decrease. The decrease in OR estimates over time was smaller for global cognition, followed by executive function, and then by episodic memory.

DISCUSSION Our findings indicate that overall performance on a brief cognitive test battery and on tests measuring specific cognitive functions differ substantially on average between those who subsequently develop clinically evident AD dementia and those who remain free of AD dementia up to 18 years before diagnosis in a biracial population sample. The results confirm that average differences in cognitive test scores between those who develop clinically evident AD dementia and those who did not can be detected up to 12 years before clinical diagnosis among European Americans.^{25,26} Our results also extend this period to the entire observation period of 18 years. Strong associations with executive

Table 5 Odds ratios for cognitive test scores of executive function, episodic memory, and global cognition predicting the development of Alzheimer disease dementia in a biracial population over an 18-year period^a

Years before diagnosis	Episodic memory ^b	Executive function ^c	Global cognition ^d
0.1–0.9	1.57 (1.48, 1.67) ^e	1.11 (1.10, 1.12) ^e	1.46 (1.39, 1.53) ^e
1.0–3.9	1.36 (1.29, 1.44) ^e	1.09 (1.08, 1.10) ^e	1.46 (1.38, 1.54) ^e
4.0–6.9	1.31 (1.23, 1.40) ^e	1.07 (1.05, 1.08) ^e	1.39 (1.31, 1.48) ^e
7.0–9.9	1.16 (1.07, 1.26) ^f	1.06 (1.04, 1.08) ^e	1.28 (1.19, 1.37) ^e
10.0–12.9	1.14 (1.02, 1.28) ^g	1.06 (1.04, 1.09) ^e	1.35 (1.20, 1.52) ^e
13.0–17.9	1.15 (1.00, 1.32) ^g	1.04 (1.02, 1.07) ^f	1.28 (1.11, 1.47) ^e

Data represent odds ratio (95% confidence interval).

^a Adjusted for age, sex, race, and education.

^b Measured using untransformed Delayed and Immediate Recall Story Test.

^c Measured using untransformed Symbol Digits Modalities Test.

^d Measured using untransformed Mini-Mental State Examination.

^e $p < 0.001$.

^f $p < 0.01$.

^g $p < 0.05$.

function and global cognition were observed at the farthest time from diagnosis (i.e., 13.0–17.9 years before) that appeared stronger than episodic memory, perhaps suggesting that loss in executive function might precede loss in episodic memory. However, the Symbol Digits Modalities Test makes demands on episodic memory as well as executive function; hence, multidimensional tests in clinical trials might be better suited to detect small changes in cognition leading to clinical development of AD dementia. Our findings are congruent with previous research that found deficits in executive and global cognition tests precede clinical diagnosis of AD dementia over 18 years and seem to exhibit deficits earlier than 15 years in visual memory performance.³⁸ More research focusing on the temporal pattern of cognitive deficits preceding development of AD dementia might provide a better understanding of preclinical stages of AD dementia.

In the development of AD dementia, pathophysiologic changes are generally thought to precede the emergence of cognitive impairment^{6,7}; in a cross-sectional analysis of parent and child, β -amyloid was detected 15 years before expected symptom onset.³⁹ Nothing in our results contradicts this idea, but if the pathologic changes of preclinical AD dementia precede emergence of the average cognitive differences we were able to detect between those who later developed clinical AD dementia and those who did not 18 years before clinical diagnosis, then the processes that constitute preclinical AD dementia may span a very long duration as suggested in biomarker studies. Our findings suggest that midlife studies might help in providing a better clinical understanding of the earliest manifestations of the disease process. Clinical studies need to be long enough to observe changes in pathologies for

clinically significant AD dementia. It is noteworthy that average cognitive differences between those who subsequently developed clinical AD dementia and those free of AD dementia were detectable both with the composite score based on multiple tests and with the individual tests, including the Mini-Mental State Examination, a test sensitive to the cognitive changes of AD dementia.

For the composite cognitive test score, ORs for the subsequent development of clinical AD dementia were higher among European Americans than among African Americans although robustly positive in both racial/ethnic groups. The basis of this racial difference is uncertain. It is possible that the temporal course of cognitive changes in AD dementia differs between African Americans and European Americans. Racial differences in quality of education could have affected our findings, but we stratified our OR estimates to adjust for race differences in education quality. In addition, in sensitivity analysis, substituting early-life cognitive activity for educational attainment yielded slightly lower ORs, and substituting early-life household socioeconomic and community socioeconomic level for educational attainment yielded slightly higher OR, with cognitive function scores still associated with clinical AD dementia over the entire duration of the study (data not shown).

This investigation has both strengths and weaknesses. The strengths include that it was of large size, conducted in a clearly defined, well-characterized sample of the general population, included adequate numbers of both African Americans and European Americans for meaningful analysis, and had a lengthy follow-up observation, whereas much of our current knowledge of preclinical AD dementia is derived from shorter-term observation of European Americans recruited at academic medical centers. Clinicians evaluating persons for the presence of clinically manifested AD dementia were rigorously masked to the results of previous cognitive testing, reducing the potential for observer bias to influence the results. Although a more extensive cognitive testing battery may be more sensitive to cognitive changes in the early stages of AD dementia, this potential weakness implies that our findings were conservative. Participants with clinical evaluations had higher cognitive scores than did nonparticipants, likely making our estimates conservative. Participants could have developed clinical AD dementia years before our clinical evaluation. However, we removed participants with suspected prevalent AD dementia from our analysis. The results from this study of a population sample from neighborhoods in a single midwestern US city may not generalize to other settings. However, both of these factors would tend to lead to falsely negative conclusions rather than the robustly positive results found.

Our results indicate that performance on a brief cognitive battery and on the cognitive domains measured by individual tests in the battery differs substantially between those who will subsequently develop clinically evident AD dementia and those who will not up to 18 years before diagnosis in a biracial population sample. If, as widely hypothesized, evidence of AD dementia pathophysiology precedes cognitive impairment in preclinical AD dementia, these results imply a very long duration for the prodromal phase of clinical manifestation of AD dementia, one that may span decades.

AUTHOR CONTRIBUTIONS

Dr. Rajan designed and conceptualized the study, conducted data analysis, interpreted the findings, and drafted and revised the manuscript. Dr. Wilson designed and conceptualized the study, reviewed and revised the manuscript. Dr. Weuve reviewed and revised the manuscript. Dr. Barnes reviewed and revised the revision of this manuscript. Dr. Evans designed and conceptualized the study, reviewed and revised the manuscript, and supervised the study.

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