

Patterns of Cognitive Decline in Presymptomatic Alzheimer Disease

A Prospective Community Study

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Background: Specific patterns of decline over time were evaluated across a spectrum of cognitive measures in presymptomatic Alzheimer disease (AD) within a community sample.

Methods: A total of 551 individuals completed a battery of standard cognitive tests 3.5 and 1.5 years before outcome (clinical onset of AD vs continued nondemented status) within a prospective community-based study of AD. Test score changes in 68 cases (who subsequently developed symptomatic AD) and 483 controls (who remained nondemented) on each of 15 cognitive measures were transformed into *z* scores adjusted for age, sex, and education. A case-control rate ratio of the proportions of individuals who showed “cognitive decline” on each test was calculated, representing the relative magnitude of cognitive decline on each test in presymptomatic AD compared with normal aging.

Results: Declines in Trail-Making Tests A and B and Word List delayed recognition of originals and third immediate learning trial had the highest rate ratios, larger than 3.0 ($P < .01$). These were followed by Word List delayed recognition of foils and delayed recall, Consortium to Establish a Registry for Alzheimer’s Disease Praxis, Clock Drawing, the Boston Naming Test, and Orientation, with rate ratios between 1.7 and 3.0 ($P < .05$).

Conclusions: Memory and executive dysfunction showed the greatest decline over time in individuals who would clinically manifest AD 1.5 years later. These findings might help us understand the underlying evolution of the early neurodegenerative process. They highlight the importance of executive dysfunction early in the disease process and might facilitate early detection of AD.

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IN ALZHEIMER disease (AD) and other chronic diseases, it is hard to ascertain how long the underlying pathological disorder has been present before clinical manifestations become apparent. Very mild cognitive impairments might be objectively identifiable in the presymptomatic or preclinical phase of AD.¹⁻⁶ Reliable, objective means of early detection would allow incipient AD to be identified not only before clinical diagnostic criteria are fulfilled but even before the first symptoms appear and would play an important role in potential early intervention.

Several studies⁷⁻¹¹ have made cross-sectional comparisons of one-time cognitive function between nondemented elderly persons and those with dementia after, and even shortly before, symptomatic onset and diagnosis. However, dementia is defined as “decline of memory and other cognitive functions in comparison with the patient’s previous level of function,”¹² implying a change between 2 or more assessment points. Evaluation of dynamic change over time, by account-

ing for potential confounders, is theoretically and clinically more meaningful than a single assessment. The progressive deterioration characteristic of AD might affect different cognitive functions at different periods during its course,^{7,13-17} as would be expected from the pathological evolution of the disease.¹⁸

See also page 859

Few previous studies¹⁹⁻²¹ empirically evaluated patterns of cognitive decline in presymptomatic AD. In a prospective community-based study,²² we compared changes over time on a spectrum of cognitive measures between 2 groups of nondemented cohort members: cases who subsequently developed symptomatic AD and controls who remained nondemented. Use of a longitudinal case-control design, within a cohort study of AD, minimized temporal and recall bias²³ and enabled us to compare cases and controls at a time when they were all symptom free. Such data might also have relevance for the evolving concept of mild cognitive impairment.²⁴

SUBJECTS AND METHODS

STUDY DESIGN AND SUBJECTS

The sample was derived from a community-based, multi-wave, prospective study—the Monongahela Valley Independent Elders Survey (MoVIES)—in southwestern Pennsylvania.²² At study entry (baseline [wave 1]), the MoVIES cohort included 1422 subjects representing a 1:13 age-stratified sample randomly selected from voter registration lists. Entry criteria included age of at least 65 years, not institutionalized at the time of recruitment, and fluent in English, with a minimum sixth-grade education. The MoVIES cohort has been followed up prospectively in a series of data collection “waves” at approximately 2-year intervals. The present analyses excluded prevalent dementia cases ($n=121$), ie, those individuals with symptomatic onset of dementia before study entry, and 6 demented individuals with uncertain onset, leaving a total of 1295 nondemented subjects “at risk” for developing incident dementia during follow-up. At the time of the present analyses, 153 of these 1295 at-risk subjects had developed incident AD during 5 waves of follow-up. Forty-six subjects who developed non-AD dementias were excluded from these analyses. Informed consent for all study procedures was obtained according to methods approved by the institutional review board of the University of Pittsburgh, Pittsburgh, Pa.

COGNITIVE SCREENING

At each wave, every subject underwent in-home screening with the same battery of cognitive tests (see the “Outcome and Predictors” subsection). Descriptions and population norms for the MoVIES cognitive test battery, test scores in demented and nondemented participants at baseline, and the utility of these tests for screening have been reported previously.^{10,25,26} At each follow-up wave, based on screening scores, 3 groups were selected for further clinical evaluation: (1) those who were “cognitively impaired,” (2) those who had “cognitively declined” since previous waves, and (3) a subgroup of cognitively unimpaired controls randomly selected at baseline.²² Briefly, the cross-sectional operational criteria for cognitive impairment were scores at or below the 10th percentile of the MoVIES sample on the Mini-Mental State Examination (MMSE) or on at least 1 memory test and 1 other cognitive test.

During follow-up, the longitudinal operational criterion for cognitive decline was a decline in scores since an earlier wave by an amount greater than or equal to the decline experienced by 95% of the sample or a decline in scores to levels below the impairment criteria described earlier.

IDENTIFICATION OF SUBJECTS WITH DEMENTIA

In-home clinical evaluations²² were performed, blind to the screening cognitive data according to the standardized protocols of the Alzheimer’s Disease Research Center at the University of Pittsburgh and the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD),²⁷ which were modified for field use. The MoVIES protocol included a standardized general medical history and a general physical examination; detailed neurological and mental status assessments; psychiatric examinations; laboratory studies for relevant hematologic, chemical, and serologic evaluations; and neuroimaging when possible and appropriate. Relevant medical records were obtained and abstracted. Final diagnosis was made by consensus, using the Alzheimer’s Disease Research Center protocol, among all evaluating clinicians and using all available data. Because the study began in 1987, the diagnosis of dementia was made according to *DSM-III-R* criteria²⁸ and according to the Clinical Dementia Rating Scale,²⁹ for which CERAD provides a scoring algorithm based on functional (rather than cognitive) impairment. Diagnosis of probable and possible AD was made according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria.¹² Once the diagnosis of dementia was made, the date of symptomatic onset was estimated retrospectively using all available evidence as to the time of emergence of symptoms of cognitive and functional decline.¹¹

SELECTION OF CASES AND CONTROLS

Selection criteria for cases were (1) development of incident AD during the 10-year follow-up period, with a mean \pm SD date of symptom onset within 1.5 ± 1.0 years of their most recent cognitive assessment date, ensuring that cases were in the presymptomatic phase of AD at the time of cognitive testing, and (2) completion of all cognitive tests 3.5 years (time 1 [T1]) and 1.5 years (time 2 [T2]) before symptom onset, ensuring that the change in performance of all individuals could be compared on all cognitive measures. Among the 153 incident cases of AD identified during

RESULTS

DESCRIPTIVE CHARACTERISTICS OF THE STUDY POPULATION

Compared with controls, cases were significantly older and a significantly higher proportion of them had low education levels (**Table 1**); there was no significant sex difference. Scores on the MMSE declined significantly more during the 2 years from T1 to T2 in cases (from 26.68 to 25.94) than in controls (from 27.76 to 27.61).

MEAN COGNITIVE CHANGE AMONG AND BETWEEN CASES AND CONTROLS

Among controls, there were no significant cognitive changes between T1 and T2 on 10 of the 15 cognitive tests; mean age-, sex-, and education-adjusted z score was approximately 0, between -0.1 and $+0.1$ ($P > .05$, within-group paired t tests). Significant improvement over time was seen on the 5 remaining cognitive tests: Word List first and third immediate learning trials, delayed recall, and delayed recognition of originals ($P < .01$ for all) and Trail-Making Test A ($P < .05$), with mean z scores between 0.1 and 0.22.

the study, 120 (78%) completed all neuropsychological tests at their T2 assessments; of these 120 cases, 68 (57%) also had complete neuropsychological test data at their T1 assessments. These 68 individuals comprised the case group.

Selection criteria for controls were (1) remaining nondemented during the 10-year follow-up period, thus ensuring that subjects with incipient dementia were not inadvertently misclassified as controls, and (2) completing all cognitive tests at waves 1 through 4, ensuring that case and control performance could be compared on all tests. Among the 1096 subjects who were not diagnosed as having dementia during 10 years of follow-up, 483 completed all neuropsychological tests at waves 1 through 4, thus comprising the control group.

OUTCOME AND PREDICTORS

The outcome variable in the analyses was symptomatic onset of AD in cases vs maintenance of nondemented status in controls 1.5 years after the most recent cognitive screening (T2). Predictor variables were changes on 15 cognitive test scores (see the next paragraph) between the 2 assessment points preceding the outcome. This was further operationalized in cases as changes in cognitive performance between the assessment points 3.5 years (T1) and 1.5 years (T2) before symptomatic onset, and in controls as changes in cognitive performance between wave 2 (T1) and wave 3 (T2) (the midpoint of 10-year follow-up of the overall study). For cases, T1 and T2 could have occurred at any 2 consecutive waves (**Figure 1**).

Predictor variables were the following neuropsychological tests: the CERAD 10-item Word List (first and third immediate learning trials, delayed recall, delayed recognition of originals, and delayed recognition of foils)²⁷; Story Recall (immediate and delayed)³⁰; Trail-Making Tests A and B³¹; Category Fluency³²; Initial Letter Fluency³³; the Boston Naming Test (15-item CERAD version)³⁴; CERAD Praxis³⁵; Clock Drawing³⁶; and the time/place orientation subtest of the MMSE.³⁷ These tests were part of the MoVIES cognitive screening battery, developed to assess several cognitive functions known to be affected in dementia²⁵ and incorporating the CERAD neuropsychological panel.²⁷

STATISTICAL METHODS

Statistical software (SAS version 6.12) was used for data analysis.³⁸ All tests were 2-tailed, with statistical significance

set at $\alpha = .05$. For descriptive statistics, differences between groups were tested using χ^2 tests for categorical data and *t* tests for continuous variables. The scales of individuals' scores on all cognitive tests were rendered uniform and were adjusted for age, sex, and education as follows. Controls' raw scores at baseline (wave 1) were transformed into normally distributed *z* scores using the formula (raw score - mean)/SD on each test. By substituting T1 and T2 raw scores into the same formula, "observed" *z* scores were calculated for cases and controls for each test at T1 and T2. A multiple linear regression model was fit for each test, with controls' baseline *z*-transformed scores as the dependent variable and age, sex, and education as the independent variables, generating coefficients (β values) for age, sex, and education for each test. "Predicted" *z* scores were then calculated for each subject on each test by entering the individual's age, sex, and education level, multiplied by the respective coefficients, into the model. Case and control test scores at T1 and T2 were transformed into age-, sex-, and education-"adjusted" *z* scores by subtracting predicted *z* scores from observed *z* scores.^{39,40} Change in cognitive scores was then measured by subtracting adjusted T2 scores from adjusted T1 scores on each test for each individual.

Despite efforts to retest subjects at 2-year intervals, the actual mean \pm SD interval between T1 and T2 was 783 \pm 91 days in cases and 822 \pm 123 days in controls. Change in test scores was standardized to 2-year cognitive change using the formula [(T1 score - T2 score)/(days between T1 and T2)] \times 730.

For inferential statistics, 2 strategies were used. First, the direction and amount of change on each test between T1 and T2 was tested for significance using paired *t* tests within case and control groups separately. On each cognitive test, the mean change observed in cases was then compared with the expected mean change, ie, that observed in controls, using *t* tests between groups. Second, each individual was categorized as "cognitively declined" or "cognitively nondeclined" on each test. Cognitive decline was uniformly defined across all tests as a cognitive decline (*z* score) of at least 1 SD greater than the mean decline in controls.⁷ A rate ratio was then estimated as the case-control ratio of the proportion who declined on each test, representing the relative magnitude of cognitive decline on each test. The contingency table method (χ^2 test) was used to test for significance of differences in proportions between cases and controls.

Among cases, performance on Trail-Making Test B on average declined the most, with mean change in *z* score being 0.88, followed by CERAD Praxis, Trail-Making Test A, MMSE Orientation, Word List third learning trial ($P < .01$ for all), Word List delayed recall, Clock Drawing, and Category Fluency ($P < .05$ for all), with the mean decline in *z* score being greater than 0.2.

Significant differences in mean T1-T2 decline between cases and controls were seen in Trail-Making Test B and A, CERAD Praxis, Word List third learning trial, Word List delayed recall, Word List delayed recognition of originals, Word List first learning trial, MMSE

Orientation, and Category Fluency ($P < .05$, *t* tests) (**Table 2**).

COGNITIVE DECLINE IN CASES AND CONTROLS

The highest case-control rate ratios, greater than 3.0 ($P < .01$), were observed for cognitive decline in Trail-Making Tests B and A and Word List delayed recognition of originals and third learning trial, followed by Word List delayed recognition of foils and delayed recall, CERAD Praxis, Clock Drawing, the Boston Naming Test, and Orientation, with rate ratios of 1.7 to 3.0 ($P < .05$). Declines

on the remaining tests had the lowest rate ratios, ie, less than 1.7 ($P > .05$) (**Figure 2**).

COMMENT

Our prospective community study afforded several advantages over clinical studies that typically examine patients who are already symptomatic and have been diagnosed as having AD. First, by following a nondemented cohort for 10 years, during which some but not all cohort members developed AD at different times, we were able to focus on a defined time window several years before onset of symptoms and thus examine all cases at the same stage of presymptomatic disease. Second, our longitudinal assessment of cognitive change over time enabled us to study the cognitive decline pathognomonic of AD, minimizing the potential confounders encountered in the study of one-time cognitive performance. Third, we accounted for the cognitive changes of normal aging as exemplified by non-

demented controls. Fourth, we normalized test scores and adjusted them for age, sex, and education, enabling direct comparison of changes on different cognitive tests along the same scale. Fifth, our cases and controls were identified during prospective follow-up of a randomly selected community-based cohort, minimizing the selection bias associated with studying patients and controls in clinical research settings.

In our sample, cognitive decline in presymptomatic AD was not uniform across cognitive domains. Memory functions (Word List learning trial, delayed recall, and delayed recognition) and executive functions (Trail-Making Tests A and B) declined the most prominently. Because memory deficit is a cardinal diagnostic feature of AD, it was confirmatory rather than surprising to find in our own study, as in those of others,¹⁹⁻²¹ that early memory impairment was associated with subsequent onset of AD. However, consensus is lacking on the sequence of the cognitive deficits that follow, precede, or coexist with memory impairment during progression of the disease, particularly early in its course. A few previous studies of patients already diagnosed as having early AD have found memory and frontal/executive functions to be the most frequently impaired.⁷⁻⁹ In the MoVIES cohort described herein, we¹¹ previously reported that at a single assessment point 1.5 years before onset, memory (delayed recall) and executive functions (Trail-Making Tests) distinguished best between presymptomatic cases and those who would remain nondemented. We now report that decline on the same tests during the 2 preceding years (3.5 years to 1.5 years before onset) predicted the development of symptoms of AD. In the Framingham cohort,²⁰ although cognitive decline was not examined, cross-sectional measures of memory (retention) and abstract reasoning (similarities and differences) were the strongest preclinical predictors of incident AD 5 and 10 years before onset. Taken together, these findings suggest that executive dysfunction is among the earliest manifestations of AD, consistent with the hypothesis of Lafleche and Albert⁸ that “the partial degeneration of an intracortical projection system early in the course of disease could produce difficulties in tasks that require the rapid and simultaneous integration of multiple types of information.”

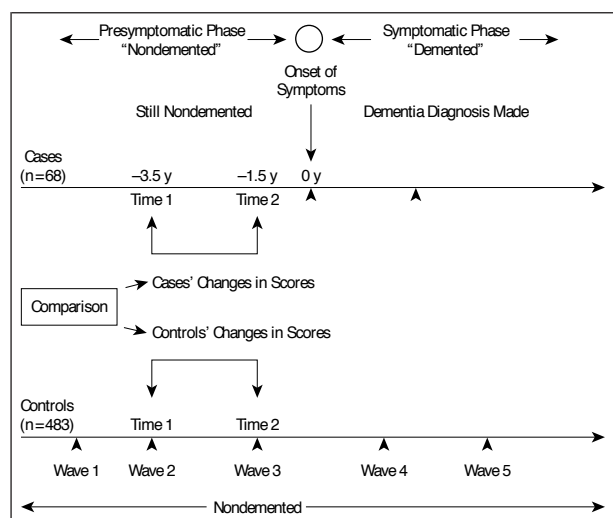


Figure 1. Design and timeline of the prospective cohort study. Case-control comparison superimposed on the course of Alzheimer disease in presymptomatic cases and a comparable period in nondemented controls. For explanations of time 1 and time 2, see “Selection of Cases and Controls” subsection of the “Subjects and Methods” section.

Table 1. Characteristics of Cases and Controls: Demographics and Change in MMSE Score*

Variables	Controls (n = 483)	Cases (n = 68)	Test for Difference†	
			χ^2 or t	P
Women, No. (%)	302 (62.5)	39 (57.4)	0.68 (χ^2_{1})	.41
Less than a high school education, No. (%)	154 (31.9)	32 (47.1)	6.14 (χ^2_{1})	.01
Age at time 1, No. (%)				
65-74 y	340 (70.4)	25 (36.8)	37.93 (χ^2_{2})	<.001
75-84 y	140 (29.0)	39 (57.4)		
≥ 85 y	3 (0.6)	4 (5.9)		
Age, mean (SD), y	72.6 (4.4)	76.6 (5.3)	5.86 (t_{90})	<.001
MMSE mean (SD) score change from time 1 to time 2‡	-0.14 (1.61) ($P = .52$)§	-0.76 (2.37) ($P = .02$)§	2.09 (t_{76})	.04

*MMSE indicates Mini-Mental State Examination. For explanations of time 1 and time 2, see “Selection of Cases and Controls” subsection of the “Subjects and Methods” section.

†Between-group comparisons based on t or χ^2 tests as appropriate.

‡Negative change scores indicate declines during 2 years, from 3.5 to 1.5 years before outcome (ie, development of clinical onset of Alzheimer disease vs maintenance of nondemented status).

§Within-group tests of significance of longitudinal change based on paired t tests.

Table 2. Two-Year Mean Cognitive Changes in Cases and Controls From 3.5 Years (T1) to 1.5 Years (T2) Before Outcome*

Cognitive Measures	Mean ± SD Change in z Scores (Raw Scores at T1 and T2)		Case-Control Difference†	
	Controls (n = 483)	Cases (n = 68)	t‡	P
Trail-Making Test B	0.07 ± 0.83 (120.9 and 130.5)	0.88 ± 1.17 (157.1 and 206.9)	5.50 (t ₇₇)	<.001
CERAD Praxis	-0.09 ± 1.05 (9.69 and 9.56)	-0.79 ± 1.48 (9.78 and 8.87)	3.77 (t ₇₇)	<.001
Trail-Making Test A	0.10 ± 0.98 (44.76 and 48.02)	0.73 ± 1.34 (51.68 and 64.25)	3.73 (t ₇₇)	<.001
MMSE time/place orientation	0.08 ± 1.38 (9.70 and 9.74)	-0.50 ± 2.08 (9.69 and 9.46)	2.23 (t ₇₅)	.03
Word List (third immediate learning trial)	0.21 ± 0.95 (8.28 and 8.42)	-0.36 ± 1.05 (7.47 and 6.84)	4.57 (t ₅₄₉)	<.001
Word List (delayed recognition of originals)	0.13 ± 0.86 (9.71 and 9.77)	-0.35 ± 1.76 (9.31 and 9.01)	2.23 (t ₇₁)	.03
Word List (delayed recall)	0.20 ± 0.79 (6.97 and 7.15)	-0.21 ± 0.89 (5.56 and 4.91)	3.93 (t ₅₄₉)	<.001
Clock Drawing	-0.08 ± 1.31 (7.36 and 7.24)	-0.46 ± 1.84 (7.07 and 6.72)	1.62 (t ₇₇)	.11
Word List (first immediate learning trial)	0.22 ± 1.03 (5.05 and 5.27)	-0.05 ± 0.94 (4.15 and 3.97)	2.04 (t ₅₄₉)	.04
Category Fluency	0.00 ± 0.74 (28.15 and 27.70)	-0.21 ± 0.69 (23.41 and 21.79)	2.18 (t ₅₄₉)	.03
Boston Naming Test	0.04 ± 0.86 (14.37 and 14.36)	-0.15 ± 1.17 (13.93 and 13.75)	1.28 (t ₇₇)	.20
Story Recall (delayed)	0.02 ± 0.68 (6.41 and 6.40)	-0.15 ± 0.96 (4.26 and 3.81)	1.38 (t ₇₇)	.17
Story Recall (immediate)	0.02 ± 0.72 (6.91 and 6.97)	-0.11 ± 0.84 (5.18 and 4.88)	1.37 (t ₅₄₉)	.17
Initial Letter fluency	0.05 ± 0.65 (23.45 and 23.46)	-0.07 ± 0.67 (19.94 and 19.04)	1.38 (t ₅₄₉)	.17
Word List (delayed recognition of foils)	-0.07 ± 2.08 (9.94 and 9.93)	0.09 ± 4.52 (9.78 and 9.79)	0.29 (t ₇₁)	.77

*Change in zscore was age adjusted for sex and education and normalized to z score. Negative change scores indicate decline and positive change scores indicate improvement, except on Trail-Making Tests A and B. T1 indicates time 1; T2, time 2. For explanations of T1 and T2, see "Selection of Cases and Controls" subsection of the "Subjects and Methods" section.

†Between-group comparisons. Within-group comparisons are reported in the text.

‡Different tests have t values with difference degrees of freedom (df); pooled df = 549 when the 2 groups had equal variances, or unpooled df = 71, 75, or 77 depending on the actual variances in each group on a given test.

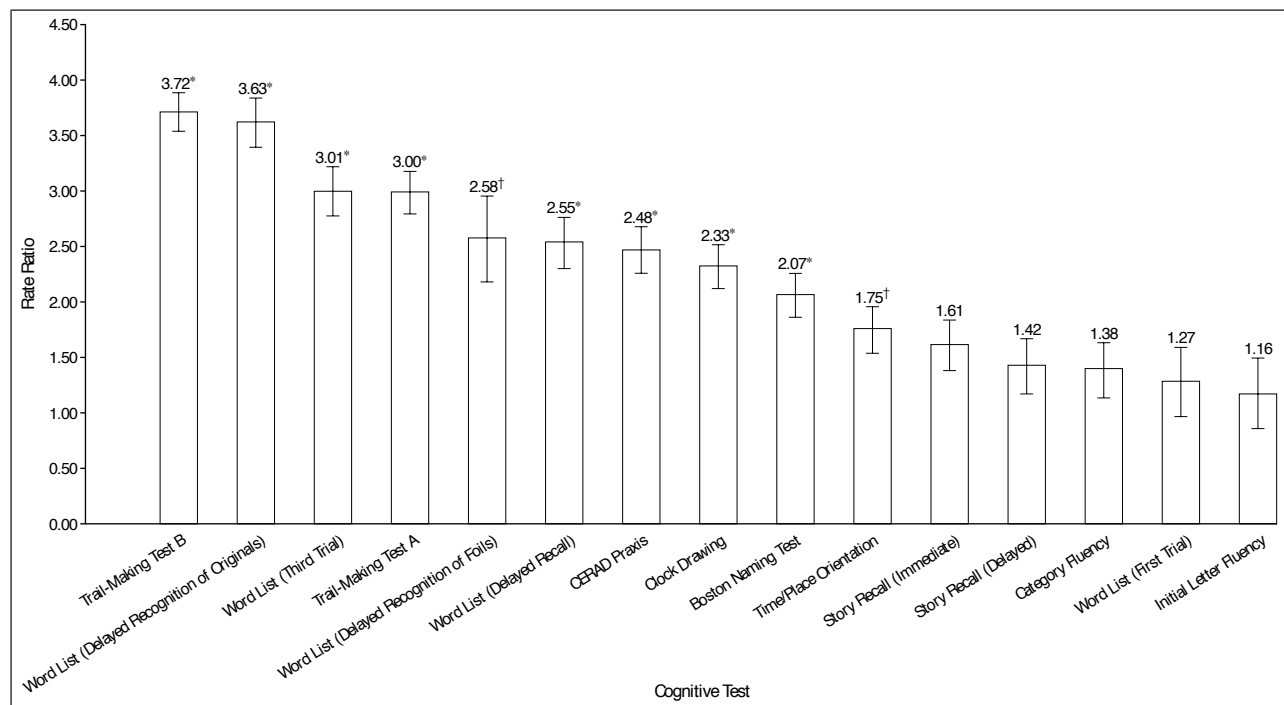


Figure 2. Patterns of cognitive decline in presymptomatic Alzheimer disease. Rate ratio of proportions of the cognitively declined among cases and controls (N=551). CERAD indicates Consortium to Establish a Registry for Alzheimer's Disease; asterisk, $P < .01$ (χ^2 test); dagger, $P < .05$ (χ^2 test). Error bars represent SE.

Early executive dysfunction might not be specific to AD, but there were too few cases of non-AD dementias (such as frontotemporal dementia)⁴¹ in our community sample to allow us to study them. Furthermore, conditions affecting visuomotor speed and attention might affect performance on the Trail-Making Test. In post hoc analyses to control for possible variation from this source, a hybrid measure, the difference between Trail-Making Tests B and A, had a rate ratio of 3.34, only slightly lower than the rate ratio of 3.72 on Trail-Making

Test B alone. Thus, our findings are most likely explained by the additional cognitive complexity and working memory "load" of Trail-Making Test B rather than the speed or visual components common to both parts A and B.

We observed small but significant presymptomatic declines in a few tasks sensitive to other cognitive changes in AD. Category Fluency is more sensitive to AD than Initial Letter Fluency, presumably because it is more affected by deterioration in the structure of semantic knowl-

edge in AD.⁴² Average performance in the CERAD Praxis test, a largely constructional task, declined 0.7 SD in 2 years, whereas Clock Drawing, involving construction and planning, declined 0.4 SD in 2 years. The case-control difference in orientation decline might be related to memory and might foreshadow the more marked disorientation characteristic of clinically evident AD.

Despite their advantages, some of our study's design features might have introduced other sources of bias. Our requirement that subjects have complete cognitive test data at multiple points might have led to our selecting a relatively "successfully aging" cohort, although cases' and controls' mean T1 MMSE scores of 26.7 and 27.8, respectively, do not suggest a substantial healthy survivor bias.¹¹ Because the same test battery was used at each wave, we cannot discount the possibility of practice effects, as demonstrated by slightly improved cognitive performance in controls on some measures. Because a true age-related improvement in cognitive function is not expected, our results might in fact underestimate any normal age-related cognitive decline, ie, practice effects might counteract age effects in nondemented elderly persons.⁴³

Our findings highlight the importance of executive dysfunction early in the disease process and might facilitate detection and monitoring of early AD. They might also help explain the temporal evolution of cognitive decline in preclinical AD and prompt further study on the underlying mechanisms.

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