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Authors

Zonderman, Alan B
Giambra, Leonard M
Arenberg, David
et al.

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Changes in Immediate Visual Memory Predict Cognitive Impairment

**Alan B. Zonderman, Leonard M. Giambra, David Arenberg,
Susan M. Resnick, and Paul T. Costa, Jr.**

National Institute on Aging, National Institutes of Health

Claudia H. Kawas

*Johns Hopkins School of Medicine and National Institute on Aging,
National Institutes of Health*

Six-year changes in immediate visual memory performance assessed by the Benton Visual Retention (BVR) test predicted Alzheimer's disease (AD) prior to its onset. Subjects of this study were 371 community-dwelling adult participants in the Baltimore Longitudinal Study of Aging, seven of whom received probable or definite AD diagnoses using DSM-III-R and NINCDS-ADRDA criteria. Subjects with diagnoses of AD had larger changes in immediate memory performance over the 6-year interval prior to the estimated onset of their disease than subjects without AD. Six-year longitudinal change as well as level in immediate visual memory performance also predicted subsequent cognitive performance 6–15 and 16–22 years later, even after adjusting for the influences of age, general ability, and initial immediate memory. These results provide evidence that change and level in immediate visual memory performance has long-term prognostic significance over as many as 16–22 years. These results further suggest that change in recent memory performance, an important component in AD diagnoses, may be an important precursor of the development of the disease.

Address correspondence to: Alan B. Zonderman, PhD, Laboratory of Personality & Cognition, Gerontology Research Center, 4940 Eastern Avenue, Baltimore, MD 21224.

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The most frequently noted and first apparent symptom of Alzheimer's disease (AD) is an impairment in recent memory (Albert, 1981; Becker, Huff, Nebes, Holland, & Boller, 1988; Corkin, 1982). If recent memory performance is key to diagnosing AD, then it is sensible to ask whether there is long-term prognostic significance when memory declines before the onset of AD. Predicting who is at risk for AD is important because valid and reliable prediction could lead to behavioral markers for early and accurate diagnoses (Khachaturian, 1985). Similarly, assessing the risk for AD may be important for early treatment when one is developed.

Surprisingly little attention has been paid to early detection of abnormal cognitive changes in the elderly that might signal an incipient dementia. The few published studies have focused largely on the early changes in cognition once the diagnosis of AD has been made. Studies typically select mild cases of AD where duration of symptoms and onset of AD is only imprecisely estimated. Important as they are, these studies provide no information on the subtle precursors that might forecast subsequent dementia (Mitrushina, Satz, & Van Gorp, 1989).

Only a small handful of studies have attempted long-term prediction of dementia. La Rue and Jarvik (1987) found that demented individuals had poorer cognitive test performance twenty years before diagnosis than those surviving to similar ages who were not demented. They also found that demented individuals had greater declines in vocabulary and forward digit span than those who did not have diagnoses of dementia. Mazur, Fuld, Blau, Crystal, and Aronson (1990) found that the Selective Reminding Test predicted dementia 1–2 years before diagnosis in a sample of initially unimpaired community-dwelling elderly volunteers. Fuld, Masur, Blau, Crystal, and Aronson (1990) found that a brief form of the Fuld Object-Memory Evaluation was a moderately sensitive predictor of subsequent dementia (.57) and a fairly specific (.84) predictor when administered approximately 1 year before diagnosis. In a 9-year follow-up study of community-dwelling 70-year-old subjects who had no initial clinical signs of dementia, Persson, Berg, Nilsson, Svanborg (1991) found that men with subsequent diagnoses of dementia had significantly poorer scores on reasoning and perceptual speed tests than men without subsequent dementia diagnoses. They found no significant baseline cognitive differences between women with subsequent dementia diagnoses and women without dementia diagnoses. They were unable to ascertain whether the initial cognitive deficits were due to early manifestations of dementia or enduring characteristics that made them more vulnerable to the disease.

In this study, data is used from a longitudinal study of community-dwelling adults to examine whether changes in immediate visual memory performance identifies suspected cases of AD before the onset of the disease. Because of the relative paucity of AD cases in community-dwelling volunteer samples, this study also examines whether changes in immediate visual memory predict subsequent cognitive impairment 6–15 year and 16–22 years later assessed by mental status and neuropsychological tests.

METHODS

Subjects

Subjects were participants in the Baltimore Longitudinal Study of Aging (BLSA), a community-dwelling, generally healthy group of volunteers who have agreed to return for medical and psychological testing every other year (Shock et al., 1984). The sample has been recruited continuously since 1958, and the majority are: white; work in, or are retired from, scientific, professional, or managerial positions; graduated from high school or college; and are married.

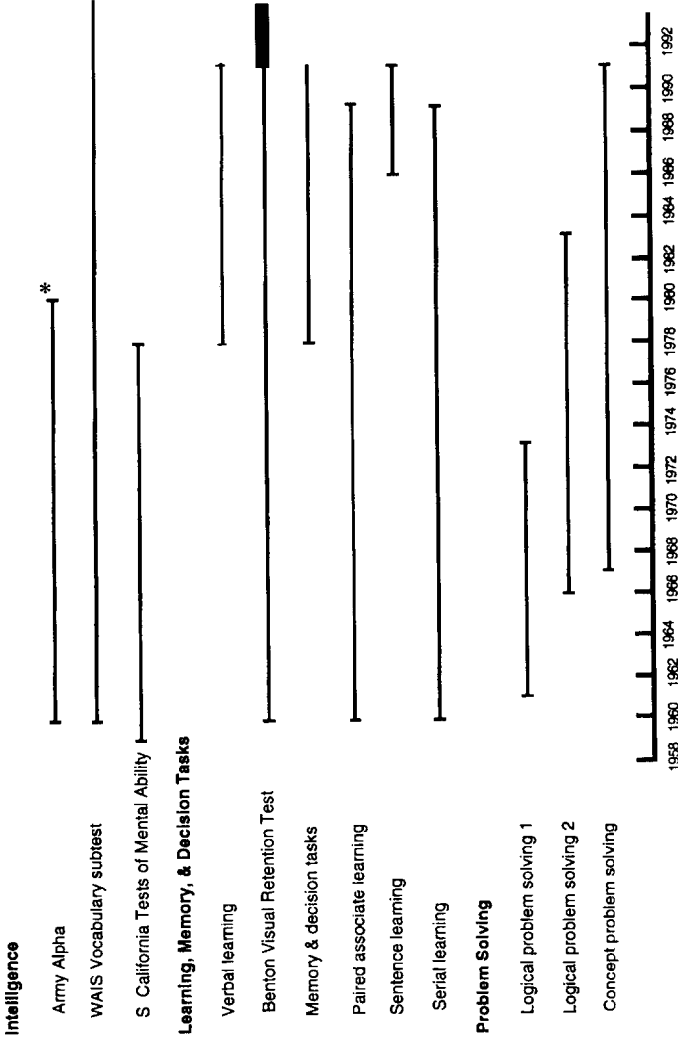
Data were available on 371 participants (254 men and 117 women) who were administered cognitive, neuropsychological, and neurological examinations between 1986 and 1992. Subjects ranged in age from 55 to 95 (mean = 72.2, *SD* = 7.6) at initial testing; men ranged in age from 55 to 95 (mean = 71.7, *SD* = 7.5), women from 59 to 90 (mean = 72.4, *SD* = 7.7).

Measures

Participants in the Baltimore Longitudinal Study of Aging have been administered cognitive tests since the study began in 1958. Although this paper focuses on two longitudinal tests that have been administered continuously since 1960, longitudinal data has been collected on a variety of other tests. As shown in Figure 1, intelligence tests, learning and memory tests, and problem solving tests have been administered at various times over the course of the study. Data on the normal course of cognitive aging have been widely published (Alder, Adam, & Arenberg, 1990; Arenberg, 1974, 1976, 1978, 1982, 1987, 1990; Arenberg & Thorne, 1976; Giambra, Zonderman, Friz, Arenberg, & Costa, 1991; Robertson-Tchabo & Arenberg, 1976, 1989; Robertson-Tchabo, Hausman, & Arenberg, 1976), but until now, little data has been available relevant to the long-term prediction of cognitive impairment. This paper examines the Benton Visual Retention Test and the WAIS Vocabulary subtests because these are tests for which the most data are available.

Participants were administered the Benton Visual Retention (BVR) test (Benton, 1974), a test of immediate recall for geometric figures. The test requires subjects to reproduce geometric designs from memory after 10 seconds of study. Each test consists of 10 separate designs with one or more figures, and the score is the total number of reproduction errors.

The BVR has been administered since 1960 and was readministered every 6–8 years (every third visit) to all longitudinal participants. Three parallel forms were administered: Form C was used for the first administration; Form E for the second; Form D for the third; Form C again for the fourth; and so on. Norms based on elderly samples have been published (Robertson-Tchabo & Arenberg, 1989), and earlier studies on BLSA subjects have shown an



*Form A was administered first; Form B was administered 6-8 years later; Form A was repeated 6-8 years after form B, after which the two forms alternated every two years.

FIGURE 1. Cognitive tests administered to participants of the Baltimore Longitudinal Study of Aging.

increase in reproduction errors with age, particularly after age 70 (Arenberg, 1978, 1982, 1987).

The WAIS Vocabulary subtest has been administered on visits concurrent with the BVR test since 1960, and was readministered every 6–8 years. Earlier studies on BLSA participants have shown great stability in WAIS Vocabulary subtest performance over as many as 18 years (Alder et al., 1990; Arenberg, 1978).

Beginning in 1986, five neuropsychological tests were administered to all subjects aged 60 and older, including two screening tests, the Mini-Mental Status Examination (Folstein, Folstein, & McHugh, 1975) and the Blessed Information-Memory-Concentration Test (Blessed, Tomlinson, & Roth, 1968; Blessed & Wilson, 1982). The Trail Making Test parts A & B (Reitan, 1958) was administered as a measure of attention and set shifting and the Cued Selective Reminding procedure (Buschke & Grober, 1986) was administered as a measure of word-list memory. This test assesses immediate recall, free recall, and 20-minute delayed recall of a list of 16 nouns.

Diagnoses of Suspected AD

In addition to cognitive and neuropsychological tests, BLSA participants also received full neurological examinations by a neurologist (CK). Subjects were considered suspected AD cases if they met DSM-III-R criteria for dementia and NINCDS-ADRDA criteria for definite or probable AD (McKhann et al., 1984; Tierney et al., 1988). Diagnoses of definite AD were based on histories of dementia and confirmation by pathology. Diagnoses of probable AD were based on relevant behavioral and cognitive performance criteria, and work-ups included CT or MRI, EEG, and appropriate serum chemistries and serologies.

Of the 371 participants in the present sample, there were 6 probable AD cases (3 women, 3 men) and one definite AD case (a man). Ages of AD onset, AD diagnoses, and total BVR errors for the suspected AD cases are shown in Table 1. (An additional subject with suspected AD was excluded because his most recent BVR was 14 years prior to the estimated date of AD onset.)

Dates of onset of disease were estimated from an informant questionnaire administered to subjects' relatives (usually a spouse or child). Specific questions included: (a) when were the first signs of memory loss noted and can you give some examples? (b) when did the subject begin making errors in activities such as financial management (checkbook, bills, taxes), cooking, and job-related activities? and (c) when was the subject last "like his or her old self" or "completely normal?" From this information, dates of onset were estimated as earliest time the disease may have begun.

The average age of AD onset was 74.1 ($SD = 9.5$) and ranged from 62 to 87 years. The average interval from the second BVR administration to the onset of AD was 2.0 years ($SD = 1.7$) and ranged from 1 to 6 years.

TABLE 1
Ages and Benton Visual Retention Test Scores at First (T1) and
Second (T2) Administrations and Estimated Ages of Onset and
Alzheimer's Disease (AD) Diagnoses

Time 1 BVR		Time 2 BVR		AD	
Age	Errors	Age	Errors	Age	Diagnosis
57	4	63	8	64	Probable
65	5	72	12	73	Probable
65	2	71	10	72	Probable
79	2	86	13	87	Probable
53	7	60	8	62	Probable
68	8	74	13	76	Probable
73	4	79	10	85	Definite

Analyses

Two sets of analyses were performed. In the first analysis, BVR scores for participants without suspected diagnoses of AD were compared to BVR scores for participants with diagnoses using repeated measures analysis of variance. For subjects without AD diagnoses, analyses were performed on scores from the last two BVR administrations. For subjects with AD diagnoses, the two most recent scores prior to their estimated date of onset were used.

In the second set of analyses, multiple regressions were used to predict mental status and neuropsychological test performance from prior BVR and WAIS Vocabulary subtest scores. Each mental status and neuropsychological test score was analyzed separately in three multiple regression models. In all three of these models, mental status and neuropsychological test scores were outcomes and the predictors were systematically varied. In the first multiple regression model, BVR change over 6–15 years predicted mental status and neuropsychological test performance after controlling for the affects of age, baseline WAIS Vocabulary, and initial BVR score. In the second, BVR change over 16–22 years predicted mental status and neuropsychological test performance after controlling for the effects of age, baseline WAIS Vocabulary, and initial BVR score. In the third, BVR scores 16–22 years prior predicted mental status and neuropsychological test performance after controlling for age and baseline WAIS vocabulary.

RESULTS

There were no significant differences between subjects with diagnoses of AD and subjects without AD diagnoses in age at initial BVR assessment (64.0 vs. 62.3 years), years between BVR tests (6.5 vs. 6.2 years), years of education (15.7 vs. 16.5 years), occupational classification (professional and managerial), or sex ratios (63% vs. 69% men).

As shown in Figure 2, subjects with diagnoses of AD had disproportionately larger changes in number of errors over the 6-year retest interval than subjects without AD diagnoses. Using repeated measures analysis of variance, there were significant mean differences between diagnostic groups ($F[1,369] = 8.0, p < .01$) as well as significant overall increases in mean errors ($F[1,369] = 37.4, p < .001$) and a significant interaction between repeated measure and diagnostic group ($F[1,369] = 23.8, p < .01$). These results suggest that in the years prior to AD onset, the immediate memory performance of subjects with suspected AD declined more rapidly than the performance of subjects without suspected AD.

These preliminary data suggest that changes in immediate memory performance may be sensitive indicators of subsequent dementia. Although there are presently too few AD cases to test this hypothesis, further examination can show whether changes in immediate memory predict subsequent performance on mental status and neuropsychological tests. The advantage to this approach is that unlike a dichotomous diagnosis, mental status and most neuropsychological tests have continuous scores so they can be used as outcome measures in prediction analyses.

A hierarchical model was constructed in which the two mental status tests and five neuropsychological tests were outcomes (dependent variables) in seven separate multiple regressions. Predictors in this hierarchical regression were entered into the model in four steps. The first step included age at neuropsychological testing (mental status examinations and neuropsychological

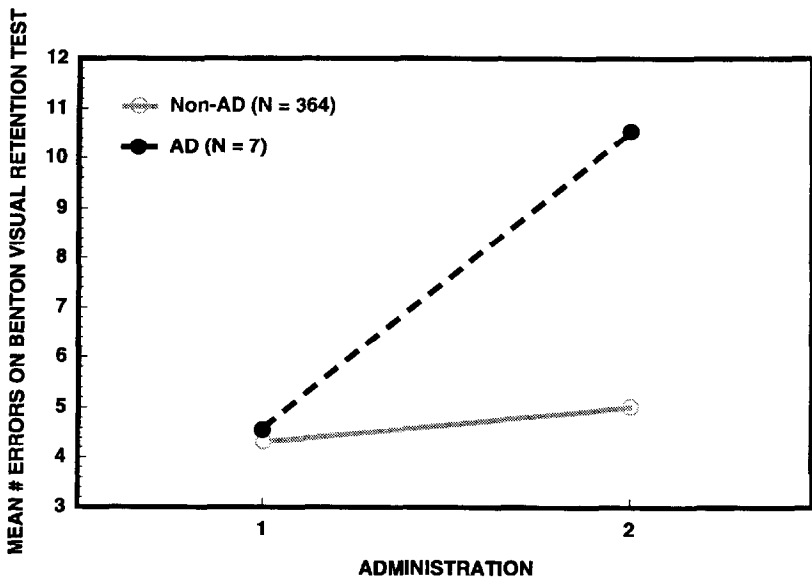


FIGURE 2. Mean number of errors on the Benton Visual Retention (BVR) test over two administrations for subjects with diagnoses of Alzheimer's disease and subjects without Alzheimer's disease.

tests were given at the same age) and the number of years between BVR testings (longitudinal interval). The second step added to the prediction model WAIS Vocabulary subtest score, a measure of general semantic knowledge and widely considered representative of general cognitive ability. The third step added initial BVR total errors, and the fourth step added to the model change in BVR total errors over the longitudinal interval.

Table 2 shows the results of predicting mental status and neuropsychological test performance from change in immediate memory performance for subjects on whom there were repeated BVR administrations approximately 6 years apart and who were also administered the neuropsychological battery between 6 and 15 years after their second BVR tests. After controlling for the influences of age (step 1) and general ability (step 2), initial BVR total errors accounted for significant variance in four of the seven tests approximately 12 years prior to neuropsychological assessment. Initial BVR total errors accounted for 5.7% of the variance of Trails A, 6.6% of Trails B, 2.9% of the Mini-mental Status Examination, and 1.7% of the Blessed IMC. After controlling for the influences of age (step 1), general ability (step 2), and initial BVR total errors (step 3), 6-year change in BVR total errors added significant variance to the prediction of six of the seven tests over the 6–15 years from last BVR to neuropsychological assessment. Six-year change in total BVR errors accounted for 5.2% of Trails B, 3.8% of the Mini-Mental Status Examination, 2.8% of the Blessed IMC, 2.3% of CSR Immediate Recall, 1.8% of CSR Delayed Recall, and 1.6% of CSR Free Recall.

A second set of analyses were performed in which the same outcomes were predicted by total errors on immediate memory for designs and 6-year change

TABLE 2
Six-Fifteen Year Prediction of Mental Status and Neuropsychological Tests from 6-Year Longitudinal Change on the Benton Visual Retention (BVR) Test^a

Predicting	N	% Variance Added in Hierarchical Regression			
		Step 1	Step 2	Step 3	Step 4
BMS	250	5.5**	2.6**	1.7*	2.8**
MMSE	250	10.1**	2.8**	2.9**	3.8**
CSR Immediate Recall	249	5.5**	0.3	0.0	2.3*
CSR Free Recall	249	3.1*	1.5*	0.8	1.6*
CSR Delayed Recall	249	1.8	1.0	0.9	1.8*
Trails A (seconds)	173	10.4**	1.7	5.7**	1.6
Trails B (seconds)	173	15.4**	6.9**	6.6**	5.2**

Note. Step 1, Age at neuropsychological assessment and number of years between testings; Step 2, WAIS Vocabulary Test; Step 3, Initial BVR total errors; Step 4, Longitudinal Change in total BVR errors. BMS = Blessed IMC; MMSE = Mini-Mental Status Examination; CSR = Cued Selective Reminding.

^aMean longitudinal interval between BVR administrations = 6.4 years (*SD* = 2.2)

p* < .05; *p* < .01.

in immediate memory for designs 16–22 years prior to neuropsychological assessment. As shown in Table 3, total BVR errors at initial testing did not account for significant variance in any of the mental status or neuropsychological tests after controlling for the influences of age (step 1) and general ability (step 2). However, 6-year change in total BVR errors accounted for significant variance in 16–22 year subsequent performance on both Trails A (4.7%) and Trails B (11.0%) after controlling for the influences of age (step 1), general ability (step 2), and initial total BVR errors (step 3).

A third set of analyses were performed in which steps 3 and 4 of the hierarchical regression were replaced by a single step consisting of the last BVR administration. In these analyses, the first step included age at neuropsychological testing; the second step added to the prediction model WAIS Vocabulary subtest score; and the third step added total BVR errors 6–15 or 16–22 years prior to neuropsychological assessment. As shown in Table 4, total BVR errors accounted for significant variance in all of the outcome measures 6–15 years later after controlling the influences of age (step 1) and general ability (step 2). Also shown in Table 4, BVR accounted for significant variance in three of the seven tests (CSR Free Recall, Trails A, Trails B) 16–22 years later.

DISCUSSION

This study used longitudinal data to examine whether subjects with AD had significantly greater changes in immediate visual memory performance prior to the estimated onset of their disease than subjects without AD diagnoses. The results suggest that subjects with diagnoses of AD had larger changes in

TABLE 3
Sixteen–Twenty-Two Year Prediction of Mental Status and Neuropsychological Tests from 6-year Longitudinal Change on the Benton Visual Retention (BVR) test^a

Predicting	N	% Variance Added in Hierarchical Regression			
		Step 1	Step 2	Step 3	Step 4
BMS	126	2.4	0.9	0.4	1.5
MMSE	126	5.3*	0.6	2.2	0.2
CSR Immediate Recall	127	4.5	1.1	1.2	0.0
CSR Free Recall	127	4.1	3.4*	1.8	2.0
CSR Delayed Recall	127	2.3	3.9	1.7	0.8
Trails A (seconds)	89	4.4	7.4**	2.8	4.7*
Trails B (seconds)	89	9.4*	8.8**	2.7	11.0**

Note. Step 1, Age at neuropsychological assessment and number of years between testings; Step 2, WAIS Vocabulary Test; Step 3, Initial BVR total errors; Step 4, Longitudinal Change in total BVR errors. BMS = Blessed IMC; MMSE = Mini-Mental Status Examination; CSR = Cued Selective Reminding.

^aMean longitudinal interval between BVR administrations = 6.5 years ($SD = 0.7$).

* $p < .05$; ** $p < .01$.

TABLE 4
Six–Fifteen Year and 16–22 Year Prediction of Mental Status and
Neuropsychological Tests from Total Errors on the Benton Visual
Retention (BVR) test

Predicting	6–15 Years		16–22 Years	
	<i>N</i>	Step 3 ^a	<i>N</i>	Step 3 ^a
BMS	250	4.3**	126	1.9
MMSE	250	6.3**	126	1.1
CSR Immediate Recall	249	2.0*	127	0.2
CSR Free Recall	249	2.4*	127	3.9*
CSR Delayed Recall	249	2.6**	127	2.0
Trails A (seconds)	173	4.4**	89	7.3**
Trails B (seconds)	173	9.4**	89	14.0**

^aVariance added by total BVR errors in Step 3 of hierarchical regression where Step 1 (not shown) included age at neuropsychological assessment and Step 2 (not shown) included WAIS Vocabulary Test.

Note. BMS = Blessed IMC; MMSE = Mini-Mental Status Examination; CSR = Cued Selective Reminding.

* $p < .05$; ** $p < .01$.

immediate memory performance over a 6-year interval prior to the estimated onset of their disease than subjects without AD. This implies that AD may be manifested by changes in memory performance earlier than is detectable by clinical evaluation.

It was also found that 6-year longitudinal changes in immediate visual memory performance predicted subsequent mental status, memory, and set shifting scores 6–15 years later even after adjusting for the influences of age, general ability, and initial immediate memory. Six-year longitudinal changes in immediate memory also predicted subsequent attention and set shifting scores 16–22 years later. Mental status, memory, attention, and set shifting scores were also predicted by immediate visual memory over 6–15 years after adjusting for the influences of age and general ability. Free recall memory, attention, and set shifting scores were also predicted by immediate visual memory over 16–22 years after adjusting for the influences of age and general ability.

These results provide clear evidence that change in immediate visual memory performance has long-term prognostic significance over as many as 16–22 years. These results further suggest that change in recent memory performance, an important component in AD diagnoses, may be an important precursor of the development of the disease. Early identification or detection of cognitive precursors of dementia might help determine whether such abnormal changes are specific or general deficits.

These results offer strong support to the value of longitudinal studies because predictions of risk for subsequent disease are possible only when baseline and follow-up data are gathered prior to the onset of disease. This is particularly important for AD. Little is known about the earliest stages of AD,

but this period is likely to be when the disease is most amenable to treatment. Therefore, early identification may be the key to preventing or at least ameliorating the disease as well as developing efficacious therapies. Longitudinal studies that have repeatedly administered cognitive tests may yield findings for the early identification of cases and may be an important source of willing participants for studies of the natural history of AD.

The results of this study indicate that substantial declines in objectively-measured memory performance are risk factors for AD and raise the possibility that such changes are early symptoms of the disease. At the least, these results suggest that severe declines in immediate memory performance might be one basis for selecting high-risk subjects for studies of the biological markers of AD. It is an open question whether changes in memory performance among the elderly represent a preclinical precursor to AD.

To the extent that the estimated age of AD onset accurately reflects the first clinical manifestation of the disease, changes in immediate visual memory performance, all of which occurred prior to the estimated onset, can be viewed as predictors of the disease. This suggests that there may be a preclinical form of AD that manifests itself in specific, and perhaps subtle, ways. For example, the results suggest that the preclinical form of AD is not a global or generalized deficit because vocabulary scores did not predict later AD. Thus, it appears that preclinical AD may be limited to specific memory functions that involve immediate recall.

Estimates of the age-specific incidence of dementia in community-dwelling populations range from less than 1 case per 1,000 person-years at age 65 to greater than 30 cases per 1,000 person-years at age 90 (Breteler, Claus, van Duijn, Launer, & Hofman, 1992). It is a reasonable expectation to find more cases of AD as the longitudinal sample ages. The present study is preliminary in that it predicts outcomes with limited cognitive data. Future research will augment both the number and types of cognitive tests as well as the number of cases.

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