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Neuropsychological indicators of preclinical Alzheimer's disease among depressed older adults

Nicole C. Rushing¹, Natalie Sachs-Ericsson¹, and David C. Steffens²

¹Department of Psychology, Florida State University, Tallahassee, FL, USA

²Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Abstract

Older adults with major depressive disorder (MDD) may also have preclinical Alzheimer's disease (AD). Differential diagnosis is quite challenging due to the over-lapping symptoms of MDD and AD. In the current study, we predicted that impaired long-term memory (an area most affected in early AD), but not executive function (an area affected in MDD and AD), would distinguish older depressed patients who developed AD from those who did not. Patients ($N = 120$) assessed as having MDD but not dementia at baseline were administered tests of cognitive function and followed longitudinally for subsequent diagnosis of AD. Using structural equation modeling we found a latent construct of long-term memory to be associated with AD to a greater extent than executive functioning. Additional analyses to enhance clinical utility of findings indicated that individual tests of episodic memory were most predictive of AD status. Tests of long-term memory can be utilized by the clinician when assessing for preclinical AD among depressed elderly.

Keywords

Alzheimer's disease; Dementia; Depression; Neuropsychological assessment

Major depressive disorder (MDD) in elderly patients is associated with mild cognitive impairment (MCI; Lee et al., 2007) and dementias such as Alzheimer's disease (AD; Jorm, 2001). Not only are depressed elderly patients at greater risk for AD than healthy controls, but MDD and AD can be difficult to distinguish because of overlapping symptoms, particularly in the initial stages of AD (Pfennig, Littman, & Bauer, 2007). Cognitive impairment in MDD may or may not represent preclinical AD. The challenge for geriatric practitioners is determining whether cognitive impairment in MDD can be ameliorated by treatment for MDD or whether cognitive impairment reflects underlying brain pathology of preclinical AD. In addition to the treatment of MDD, early identification of AD among depressed patients is important because patients might benefit from cognition-enhancing or disease-modifying drugs currently under development and assumed to have greatest efficacy in delaying symptoms early in the course of AD (Gauthier, 2005).

The current longitudinal study identified areas of cognitive function that differentiate depressed patients with preclinical AD from depressed patients who do not convert to AD. We proposed that tests of long-term memory (most impaired in early AD), but not tests of

executive function (impaired in both MDD and AD), would distinguish older depressed patients who developed AD from those who did not.

Cognitive impairment in AD

Structural and functional imaging studies of preclinical AD among older adults in general point to anatomical changes in the temporal lobe most often. Frontal and parietal lobes and the posterior cingulate of the “limbic lobe” are also affected to a lesser extent (Backman, 2009; Bondi et al., 2008; Twamley, Ropacki, & Bondi, 2006). Given the impairment in multiple brain regions in preclinical AD, it is not surprising that studies find a range of neuropsychological deficits appear up to 14 years before diagnosis of AD (Amieva et al., 2008). In fact, MCI typically characterizes the transitional state between normal cognition and dementia (Peterson et al., 2001). There is agreement that one area consistently impaired in this transitional state is long-term memory, thought to be partially mediated by the temporal lobe. In this regard, deficits on tests of verbal and nonverbal delayed recall of new information are most consistently characteristic of patients who progress to AD (Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000). Other areas of neuropsychological impairment in preclinical AD identified in a recent meta-analysis (Backman, 2009) and review (Twamley et al., 2006) include semantic memory, processing speed, executive functioning, and global cognitive functioning, but not short-term or immediate memory (Backman, 2009; Backman, Jones, Berger, Laukka, & Small, 2005; Backman, Small, & Fratiglioni, 2001) or sensory or motor abilities (Arnaiz & Almkvist, 2003).

Cognitive impairment in MDD

Cognitive impairment is also seen in older depressed patients relative to non-depressed controls in meta-analytic (Christensen, Griffiths, MacKinnon, & Jacomb, 1997) and cross-sectional studies (Austin, Mitchell, & Goodwin, 2001; Pfennig et al., 2007; Reischies & Neu, 2000), particularly in the areas of episodic memory, semantic memory, attention, short-term memory, processing speed, executive functioning/working memory, and visuospatial ability. Thus, there is considerable overlap in cognitive impairment in elderly with MDD and elderly with preclinical AD in two domains.

First, relative to healthy controls, depressed elders in general are impaired on tests related to executive function including processing speed and executive control/working memory, as well as attention and immediate memory (Nebes et al., 2003). These deficits generally improve after successful treatment of MDD, even in studies where other cognitive impairments in episodic memory may not improve (Butters et al., 2000; Devanand et al., 2003), which suggests impairment in executive function would not be predictive of preclinical AD among depressed patients.

Second, like with AD alone, patients with MDD who later convert to AD may suffer from long-term memory impairment. Importantly, this long-term memory impairment that occurs above and beyond the motivation, attention, and executive functioning deficits in MDD and does not fully improve after treatment of depression (Butters et al., 2000; Devanand et al., 2003) is likely indicative of structural changes that represent underlying AD. Although there is evidence that deficits correlated with executive dysfunction may negatively impact older depressed patients' performance on long-term memory tasks (Nebes et al., 2003), the mechanism of reversible long-term memory deficits in MDD (without preclinical AD) should differ from that of stable long-term memory deficits in MDD with preclinical AD (i.e., temporal lobe atrophy). Thus, we propose that impairment on tests of long-term memory may be useful in differentiating patients with MDD with preclinical AD from patients with only MDD (without preclinical AD).

Cognitive impairment in MDD with preclinical AD

Because differential diagnosis of MDD and preclinical AD at baseline is difficult, many studies investigating indicators of preclinical AD exclude subjects with MDD and focus on non-depressed elderly. As a result, few studies have attempted to identify cognitive tests that differentiate depressed older adults with preclinical AD from depressed older adults without preclinical AD. The results from those that have are mixed and sometimes even contradictory.

Global cognitive functioning scores on the Mini-Mental Status Examination (MMSE; Alexopoulos, Meyers, Young, Mattis, & Kakuma, 1993; Steffens et al., 2007), as well as scores on tests associated with long-term memory (Jean, Simard, van Reekum, & Clarke, 2005), appear to differentiate depressed patients who develop AD from those who do not, though results are not always consistent (Halloran et al., 1999). Methodologically, it is important to note that these studies focused on development of any dementia rather than AD specifically, which is a more heterogeneous outcome, and two (Alexopoulos et al., 1993; Steffens et al., 2007) examined a single measure of global cognitive functioning, the MMSE. Findings of general deficits on global measures of cognitive functioning may be limited in their usefulness because it is difficult to determine which domain of cognitive functioning is most impaired. Finally, follow-up periods tended to be short (for example, 2 years; Halloran et al., 1999), which may not allow sufficient time for AD to be clearly apparent.

In a most informative study, Visser, Verhey, Ponds, Kester, and Jolles (2000) gave non-demented patients several neuropsychological tests at baseline and assessed for AD over 5 years later. They excluded at baseline subjects with dementia or significant cognitive impairment. Depressed and non-depressed patients who developed AD were impaired on measures of executive functioning (fluency and time on a memory scanning task), as well as delayed recall, an episodic memory task. However, among depressed patients in particular, poorer delayed recall scores distinguished those who developed AD at follow-up. Although the executive functioning tasks were found to be impaired among the depressed group relative to the non-depressed control group at baseline, importantly, these tests were not predictive of AD among depressed patients. Thus, episodic memory (a long-term memory function) in particular predicted new cases of AD in MDD.

Currently there is no consensus as to which neuropsychological test results are most indicative of preclinical AD. There do appear to be indicators of an early transitional dementia state (MCI) in elderly patients with MDD. In one study, depressed individuals classified as MCI at baseline based on below average performance on long-term memory tests were four times more likely to be classified as MCI 1 year later despite remission of depression (Lee et al., 2007). Furthermore, using approximately the same neuropsychological battery as the current study, some have shown that verbal and nonverbal delayed recall tests best discriminate late-onset MDD from AD without MDD (Kunig et al., 2006). Taken as a whole, it is expected that the best approach for identifying depressed patients in the preclinical AD phase is to show the presence of long-term memory impairment (e.g., episodic memory, semantic memory, or orientation) that is not explained by other cognitive deficits such as those associated with executive functioning (e.g., attention/immediate memory, processing speed and executive control/working memory) associated with depressed elders in general and which may improve after the MDD remits.

Current study

The current study used data from individuals age 60+ with MDD but without apparent indicators of dementia for whom a wide array of neuropsychological tests was obtained at baseline and who were assessed each year for AD over at least a 2.5-year or longer follow-

up period. Using structural equation modeling (SEM) we developed a latent construct of *long-term memory* derived from several tests assessed at baseline which we predicted would be *strongly* related to AD status over time. We also developed a latent construct of *executive function* derived from tests thought to identify deficits in cognition related to MDD but which we predicted would have a *weaker* association to AD. Because results of the SEM may not have direct clinical utility, we also tested a hierarchical logistic regression model of individual neuropsychological tests at baseline most likely to predict AD over the follow-up period.

METHOD

Participants

Our sample consisted of depressed patients enrolled in the Neurocognitive Outcomes of Depression in the Elderly (NCODE) study, a study of adults age 60 and older at Duke University Medical Center, beginning in 1997 (Steffens et al., 2004). Participants were referred from primary care physicians, psychotherapists, or psychiatrists at Duke or in the community.

At baseline participants were excluded from the NCODE study if they met criteria for a primary diagnosis of another major Axis I psychiatric disorder that may have affected cognitive functioning (e.g., bipolar disorder, schizophrenia, schizoaffective disorder, substance abuse), endorsed history of alcohol or substance use problems, were diagnosed with a primary neurological condition (e.g., stroke, seizure disorder, Parkinson's disease), were coping with other factors/conditions that may affect neuropsychological performance (e.g., barbiturate or hypnotic use, major medical illness with cognitive sequelae, significant sensory or motor limitations), or met criteria for dementia or expected dementia (discussed later). Those with psychotic depression or comorbid anxiety disorders were included as long as the geriatric psychiatrist deemed MDD to be the primary psychiatric disorder.

There were 152 individuals who met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for current MDD at baseline and were evaluated on numerous neuropsychological tests at baseline. Among these participants, there was some attrition over time, and some ($n = 4$) were excluded because they developed a dementing illness due to causes other than AD (e.g., vascular, subcortical, Pick's disease, Lewy Body). We included patients in the current study if they were followed-up a minimum of 2.5 years based on meta-analytic studies of conversion to dementia which indicate that for patients with MCI who ultimately develop dementia, conversion is likely to occur within the first 3 years (Mitchell & Shiri-Feshki, 2008, 2009). In the current study 120 depressed patients were followed up for at least 2.5 years, and some were followed for as long as 12 years ($M = 7.1$, $SD = 2.7$).

Baseline depression assessment

At baseline a geriatric psychiatrist diagnosed MDD based on: (1) a clinical interview, (2) the Duke Depression Evaluation Schedule (DDES), and (3) a number of standardized clinical assessments, including the Montgomery Asberg Depression Rating Scale (MADRS). Trained interviewers administered the DDES, a computer-assisted structured interview that included the Diagnostic Interview Schedule (DIS) which allows for an assessment of DSM-IV current and lifetime MDD. Items on the DIS paralleled symptom criteria for DSM-IV diagnosis of MDD, specified all questions and probes to be used, and were accompanied by a set of computer programs that made diagnoses on the basis of analysis of symptom scores. The DIS has been used in a set of epidemiological studies sponsored by the NIMH Center for Epidemiological Studies and is widely used in research of aging populations (Robins,

Helzer, Croughan, & Ratcliff, 1981). It has been found to have good validity and reliability for participants of all ages (Beekman et al., 2000), with percent agreement between the lay-administered DIS and psychiatrist clinical diagnosis ranging from 79 to 96% (Helzer et al., 1985). Its accuracy has been evaluated in test–retest designs (Robins, Helzer, Croughan, Williams, & Spitzer, 1981), and for the MDD section used in the current study, reliability is at least moderate (Yule's $Y = 0.64$ for lifetime major depression; Vandiver & Sher, 1991).

Baseline cognitive screening to rule out dementia

In addition to assessing MDD, at baseline a geriatric psychiatrist examined each patient, reviewed the patient's medical records and results of the DIS assessment, and consulted with the referring physician to determine whether the patient had a diagnosis of dementia. Patients with a dementia diagnosis at baseline were not enrolled in the NCODE study.

Additionally, to identify expected dementia at baseline all patients were administered the MMSE (Folstein, Folstein, & McHugh, 1975). Depressed patients with initial MMSE scores <25 were followed through an 8-week phase of treatment to determine if cognition improved as the MDD improved (e.g., MMSE of 25+). Individuals whose MMSE scores remained <25 were not included in the NCODE study, as these patients were already experiencing cognitive difficulties potentially indicative of expected dementia. Thus, the 120 patients included in current analyses obtained a MMSE score ≥ 25 at baseline ($n = 116$) or after initial treatment ($n = 4$).

Clinical follow-up of depressed subjects

The NCODE study operates in a naturalistic treatment milieu using a treatment algorithm established by the Duke Affective Disorders program. Treatment modalities included antidepressant medication, electroconvulsive therapy, and individual and group cognitive-behavioral therapy.

AD diagnosis

Based on follow-up clinical evaluations over time, a subsample of patients possibly having cognitive problems indicative of the onset of AD was reviewed by a consensus diagnostic conference. Patients were selected into this subsample for further follow-up if the geriatric psychiatrist suspected dementia, MCI, or clinically significant cognitive decline, if the patient was given a diagnosis consistent with dementia or cognitive impairment after review of the most recent neuropsychological data (collected at approximately 1-year intervals), or if a neurological consultation resulted in a diagnosis of dementia or cognitive impairment. A consensus panel of experts in dementia, including five geriatric psychiatrists, a cognitive neuroscientist, one to two neuropsychologists specializing in memory disorders, and a neurologist specializing in memory disorders, met yearly to review patients meeting these criteria at any point during the study.

At each conference the treating study psychiatrist presented the case, the neuropsychologist reviewed the most recent neuropsychological findings, panel members reviewed initial and most recent depression study notes and neurological consultations when available, and the panel discussed each case until a consensus cognitive diagnosis was reached. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA Alzheimer's criteria for diagnosis (McKhann et al., 1984). Panel members used these criteria for diagnoses of probable and possible AD or other dementia (Roman et al., 1993). These criteria have shown good reliability and validity (Blacker et al., 1994). In addition, subsyndromal AD was defined as early or prodromal stages of AD and included functional

impairment in one or more cognitive domains clinically suggestive of early AD (Steffens et al., 2004) and is somewhat broader than MCI. The dependent variable was coded 1 (probable, possible, or subsyndromal AD) or 0 (no dementia).

Patients who have not been selected to be reviewed by the consensus diagnostic conference are those whose study geriatric psychiatrist has not identified a cognitive problem after a complete review of the most recent records. Any patient whose case was not reviewed at a consensus diagnostic conference or was not assigned a dementia diagnosis over the follow-up period was coded 0 (non-AD case). Thus, those cases deemed “normal/non-case” and those with “cognitive impairment, no dementia” (those with cognitive impairment by report or on testing but with mild or no functional impairment) were coded 0.

Neuropsychological test battery

The neuropsychological test battery was administered at baseline and in intervals of approximately 1 year if patients could be reached for follow-up. It consisted of a brief screening battery for dementia, the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD), supplemented by additional measures that correspond to several domains of cognitive functioning to enhance detection of early dementia. For the current study, we examined tests at baseline known to be associated with preclinical AD and eliminated tests not impaired in preclinical AD (e.g., tests sensitive to sensory and motor disabilities). Testing was administered by a trained psychometric technician supervised by a licensed clinical neuropsychologist and took approximately 60 minutes. To minimize possible fatigue effects, subjects received a 5-minute rest period after 20 minutes of testing.

Tests of long-term memory

Episodic memory: Episodic memory includes recall of specific events and experiences. Lesions of the temporal lobe are associated with disrupted episodic memory (Lezak, Howieson, & Loring, 2004).

WMS-R Logical Memory Delayed Recall: The Wechsler Memory Scale-Revised (WMS-R) Logical Memory Delayed Recall assessed delayed verbal memory (Wechsler, 1987). The patient was asked to repeat as many details from two orally presented narratives as possible, first for an immediate recall trial, and second for a 30-minute delayed recall trial and was awarded one point for each correctly recalled detail (range 0–50).

CERAD Word List Learning Delayed Recall: Word List Learning Delayed Recall assessed learning ability for new verbal information (Morris et al., 1989). Ten nouns were simultaneously read aloud by the examiner and shown from a booklet one at a time for 2 seconds to ensure that the patient understood each word. The same 10 words were presented in a different order for three trials. The number of correctly recalled words after a 10-minute delay filled with a nonverbal distracter task was recorded. One point was given for each correctly recalled word (range 0–10). We included delayed recall rather than the recognition version of this subtest due to previous findings that delayed recall best discriminated MDD from AD (Kunig et al., 2006).

CERAD Constructional Praxis Delayed Recall: Constructional Praxis Delayed Recall measured nonverbal memory. Patients were asked to draw the four geometric figures from the Constructional Praxis test approximately 4 minutes after their initial drawings (Yuspeh, Vanderploeg, & Kershaw, 1998). Patients were awarded one point for each detail correctly drawn (range 0–11).

MMSE delayed recall items: Patients were asked to recall three words (apple, table, and penny) they were told earlier in the examination and awarded one point for each correctly recalled word (range 0–3; Folstein et al., 1975).

Semantic memory: Semantic memory refers to what is learned as knowledge. Semantic disruptions in preclinical AD appear in verbal fluency, or the ability to say as many words as possible belonging to a certain category within a certain amount of time, as well as confrontation naming, or the ability to name objects presented in pictorial form. The temporal lobe (e.g., perirhinal cortex) is associated with semantic errors and retrieval of semantic information, and the hippocampus is related to visual confrontation naming (Sawrie et al., 2000).

CERAD Category Fluency: Patients were asked to generate words that belonged to a specific category (i.e., animals). The total score was calculated by summing the number of words the subject produced each 15 seconds. Repetitions of the same word, and words outside the category were not counted.

CERAD Boston Naming Test: The Boston Naming Test is a measure of confrontation naming ability (Kaplan, Goodglass, & Weintraub, 1978) that contains five high, medium, and low frequency items. The examiner presented patients with a series of black and white drawings and asked them to provide the name of the object. Ten seconds were allowed for each picture. Each correct response, including a correct response after semantic cue, was given one point (range 0–15).

Orientation: Orientation refers to the awareness of self in relation to one's surroundings. Both temporal and spatial disorientation in AD are correlated with degeneration (i.e., neurofibrillary tangle densities) of pathways linking the hippocampus with the superior parietal and posterior cingulate cortex in the right hemisphere (Giannakopoulos et al., 2000).

Orientation to place was assessed with the MMSE orientation items (Folstein et al., 1975) by asking for the state, county, city, floor of building, and address. Temporal orientation was assessed by asking for the year, season, date, day of week, month. Responses to each question were coded 1 (correct) or 0 (incorrect) and then summed (range 0–10).

Tests of executive function—The domain of executive functioning is broadly defined across studies, but generally includes higher-order cognitive processes like attentional control, planning, working memory, performance monitoring, and mental flexibility and appears to be related to regions of the frontal lobe, prefrontal cortex, and subcortical structures.

Attention/Immediate memory: Immediate memory refers to the capacity for holding a small amount of information in mind in a readily available state for a short period of time and can be thought of as simple, immediate span of attention (Lezak et al., 2004). Immediate memory is associated with the dorsolateral prefrontal cortex of the frontal lobe.

The Benton Visual Retention Test (Benton, 1974) is an un-timed test measuring immediate visual perception and memory and has been included in other studies of executive function (Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004). Each of the 10 designs was shown for 10 seconds, and the patient was asked to draw the design on paper immediately after removing the stimulus. Results were scored by form, shape, patterns, and arrangement on the paper (correct/incorrect; range 0–10).

Processing speed: Processing speed is the ability to automatically and fluently perform cognitive tasks, especially when high mental efficiency is required. Processing speed is associated with activity in the prefrontal cortex of the frontal lobe (Rypma et al., 2006).

The Symbol Digit Modalities Test assessed attention, processing speed, and incidental memory. Patients used a key showing nine number and symbol pairs to write a series of numbers matching their corresponding symbols (Smith, 1982). The total number of correct responses within 90 seconds was recorded, with a maximum score of 110.

Executive control/working memory: Working memory requires people to hold information in mind while performing a mental operation on it via executive processes (such as decision making and attentional control); thus, in the current study we considered working memory tasks to fall under the domain of executive control.

Trail Making Test Part B – Part A: Part A of the Trail making Test required patients to quickly connect numbered circles ranging from 1 to 25 scattered on a page in sequence, whereas Part B assessed attention, visuomotor processing speed, and mental flexibility by requiring patients to connect circles in alternating numerical (1–13) and alphabetical (A–L) sequences (Reitan & Wolfson, 1985). Completion time in seconds was recorded with a maximum of 300 seconds. We computed the difference in seconds on Parts B and A, which minimizes the influence of visuomotor tracking on Part B performance and is a purer measure of executive control and working memory (Strauss, Sherman, & Spreen, 2006).

WAIS-R Digit Span Backward: Digit Span Backward (Wechsler, 1981) is a test of working memory and mental tracking which involved presenting a series of digits out loud at a rate of one per second. The patient was then asked to repeat the digits in backward order (range 0–14).

Ascending Digit Span: Ascending Digit Span was modeled after the Digit Ordering Test. The examiner read a series of numbers and asked the patient to reorder the numbers in ascending order from smallest to largest (Sair, Welsh-Bohmer, Wagner, & Steffens, 2006). Participants were read lists ranging from 2 to 8 numbers and allowed a maximum of two tries at each level. The task was stopped if the patient made two errors at a given level or completed eight digits correctly. Scores range from 0 to 14.

MMSE attention item: Patients were asked to spell “world” backwards and awarded one point for every correct letter (range 0–5; Folstein et al., 1975).

Control variables

Variables associated with poorer cognitive functioning or AD including advancing age (Kawas & Katzman, 1999), fewer years of education (Ott et al., 1995), non-Caucasian race (Sachs-Ericsson & Blazer, 2005), and female gender (Fratiglioni et al., 1997) were assessed at baseline and controlled for in logistic regression analyses. In addition, we also controlled for indicators of MDD severity from the DDES including age of MDD onset, number of depressive episodes, and number of current DSM-IV depressive symptoms on the DIS.

Data analytic plan

We used SEM in Mplus (Muthén & Muthén, 2004) to relate baseline scores on neuropsychological tests to AD status over the follow-up period (see Figure 1). Given the wide range of neuropsychological impairment in preclinical AD, we expected all of the tests to relate to AD status to some extent; however, we expected certain tests to be better predictors than others. The first latent predictor variable, *long-term memory*, was comprised

of tests at baseline (episodic memory, semantic memory, and orientation) hypothesized to be strongly related to AD status at follow-up. The second latent predictor variable, *executive function*, was comprised of tests at baseline (attention/immediate memory, processing speed and executive control/working memory) associated with deficits among depressed patients but not hypothesized to be strongly related to AD status at follow-up among depressed patients. To statistically compare the strength of the structure coefficients from *long-term memory* and *executive function* to AD status to determine if *long-term memory* was related to AD status to a greater extent than *executive function*, we re-ran the model constraining the structure coefficients to be equal and examined results from a chi-square difference test. Thus, the SEM was a test of our theoretical model of *long-term memory* predicting conversion to AD.

To identify tests that would be clinically useful in identifying preclinical AD we performed a hierarchical logistic regression in SPSS Predictive Analytics Software (PASW) version 18 to predict accuracy of conversion to AD based on the individual neuropsychological tests. We entered the predictors in a planned manner. Demographic variables and indicators of depression severity were entered first. Next, those test related to AD status in our theoretical model, which we predicted would be long-term memory tests, were entered, followed by executive function tests. To reduce the number of parameters to estimate, we selected the neuropsychological tests with the three highest loadings from the SEM on each latent variable (long-term memory and executive function) for this analysis. We expected long-term memory impairment would predict AD above and beyond the effects of diminished executive function seen in MDD in general. Entering the variables in this planned manner (long-term memory tests on step 2, followed by executive function tests on step 3) allowed us to examine whether the addition of the executive function tests attenuated the effect of the long-term memory tests in predicting AD status.

Standardized regression coefficients were used to compare the relative strength of the relationship between the independent variables and dependent variable because the independent variables were measured on different scales (Menard, 2010). Regression coefficients standardized on both the independent and dependent variable are not provided directly in PASW, but were calculated based on the following formula where β is the standardized regression coefficient, b is the unstandardized regression coefficient, s_X is the standard deviation of the predictor variable, s_Y is the estimated standard deviation of predicted values of $\text{logit}(Y)$, and R is the square root of the explained variance: $\beta = (b)(s_X)/s_Y = (b)(s_X)(R)/s_{\text{logit}(Y)}$.

RESULTS

Descriptive statistics

Participants in the sample for the current study ($N = 120$) were 68 years old on average and highly educated (14 years on average; see Table 1) at baseline. The majority were female and Caucasian. On average, participants had suffered their first depressive episode in mid-life (44 years old) and experienced seven depressive episodes over their lifetime. Participants were followed-up 7 years on average and 15 developed AD over the follow-up period (see Table 2).

Missing data

There were 28 participants excluded from the current study due to inadequate follow-up period. Participants not followed up had fewer years of education, 12.5 ($SD = 3.2$) vs. 14.0 ($SD = 2.8$), $F(1, 150) = 5.96$, $p = .016$, and poorer cognitive functioning at baseline as assessed by the MMSE, 27.6 ($SD = 2.2$) vs. 28.5 ($SD = 2.0$), $F(1, 150) = 4.92$, $p = .028$.

There were no differences in age, sex, race, or depression severity. Thus, these excluded participants may have been more likely to be exhibiting preclinical AD at baseline, and their inclusion may have provided further power for testing the models.

Structural equation model

Missing data—Data on some of the neuropsychological tests at baseline were missing (see Table 1). Missing data were handled using full-information maximum-likelihood (FIML), a model-based approach to account for missing data and the default method in Mplus.

Model fit—Several indices indicated model fit was good (Tucker Lewis Index [TLI] = .945, Comparative Fit Index [CFI] = .955, and Root Mean Square Error of Approximation [RMSEA] = .056).

Interpretation of structure coefficients—Standardized SEM results are displayed in Figure 1, and significance levels in Table 3. All latent variable (long-term memory and executive function) loadings were significant. For long-term memory, the standardized loadings with the highest absolute values were WMS-R Logical Memory Delayed Recall, CERAD Constructional Praxis Delayed Recall, and CERAD Word List Learning, respectively, all measures of episodic memory. Loadings are interpreted as follows: a one unit increase in the latent variable causes an x increase in the indicator. For example, a one unit increase in long-term memory caused a 0.762 increase in WMS-R Logical Memory Delayed Recall. For executive function, the standardized loadings with the highest absolute values were the Benton Visual Retention Test, the Symbol Digit Modalities Test, and Trail Making Test Part B—Part A, respectively. The residual variances of the indicators were significant, suggesting that there was unique variance in the indicators not fully accounted for by the latent variables.

The latent construct long-term memory was positively correlated with the latent construct executive function. As expected, both long-term memory and executive function at baseline were significantly associated with AD status at follow-up such that lower cognitive functioning was related to conversion to AD. Importantly, as predicted in our theoretical model, the standardized structure coefficient of long-term memory (−0.366, medium effect; Kline, 2005) was greater than that of executive function (−0.248, small to medium effect; Kline, 2005).

Chi-square difference test—To assess whether long-term memory was associated with AD to a statistically *significantly* greater extent than executive function, we compared the χ^2 values obtained from the original model ($\chi^2 = 103.123$, $df = 75$) with a second model in which the with structure coefficients to AD status from the latent variables were constrained to be equal ($\chi^2 = 106.953$, $df = 76$). This resulting χ^2 value (3.83, $df = 1$) was only slightly lower than the critical value in the χ^2 distribution table for a one df test at the .05 significance level ($\chi^2 = 3.84$). Thus, we can conclude that the unconstrained model is a marginally better fit to the data, such that long-term memory is associated with AD status to a greater extent than executive function.

Logistic regression

Prior to running the logistic regression analysis, we examined intercorrelations on test scores (Table 4). None had an absolute value greater than .80, so no tests were removed from the analysis on the basis of multicollinearity, as is the method consistent with other studies (Tierney et al., 1996; Tierney, Yao, Kiss, & McDowell, 2005).

Results are displayed in Table 5. In the step one model (demographic and depression severity variables) only two predictors, increasing age and fewer current depressive symptoms, made a unique, statistically significant contribution to the model.

The step two model (addition of long-term memory tests) was statistically significant, and the additional variables distinguished who would develop AD over and above the step one variables, $\chi^2(3, N = 108) = 9.806, p = .020$. The model explained between 24.8% (Cox and Snell R^2) and 51.4% (Nagelkerke R^2) of the variance in AD status. Of note, only one of the long-term memory tests, WMS-R Logical Memory Delayed Recall, made a statistically significant contribution to the model. For every additional point on this test, participants were 0.806 times less likely to develop AD, controlling for all other variables including age. On average, the mean of those patients who developed AD was almost 1 *SD* below the mean for the AD-free patients.

The step three model (addition of executive function tests) was statistically significant, but not over and above the step two model, $\chi^2(3, N = 108) = 2.241, p = .524$. Consistent with hypotheses, none of the executive function tests made a statistically significant contribution.

Calculated standardized regression coefficients for the neuropsychological tests appear in Table 6. We also computed standardized coefficients based on models with only the single neuropsychological test predicting AD status. As predicted, the three long-term memory tests (CERAD Word List Learning Delayed Recall, WMS-R Logical Memory Delayed Recall, and CERAD Constructional Praxis Delayed Recall, respectively) emerged as the standardized predictors with the highest absolute values. For clinical guidance, in Table 1 we report the mean score on each test for the group who developed AD compared to the group who did not.

DISCUSSION

A body of literature has shown that depressed older adults who currently show no overt clinical indications of dementia are nonetheless at particularly high risk for AD. Jorm (2001) summarized the most viable explanations to account for this association between depression and AD: (1) depression acting as a chronic stressor increases risk for AD by damage to the hippocampus, an area of the temporal lobe associated with learning and memory and damaged early in the course of AD, via a glucocorticoid cascade (Sapolsky, Krey, & McEwan, 1986), and (2) late-life depression is an early prodrome of dementia, with depressive symptoms produced by underlying neurological changes in AD (Brommelhoff et al., 2009; Janssen et al., 2007). Both explanations have received empirical support, and some suggest the relationship may be due to a combination of both factors (Andreescu et al., 2008).

Indeed, it may be the case that some older individuals who present with MDD have preclinical AD that is not apparent on initial evaluation. The purpose of the current study was to identify domains of cognitive functioning and neuropsychological tests that identify older adults with MDD who convert to AD. We presented a theoretical model in which we predicted the latent construct of long-term memory may underlie preclinical indicators of AD, whereas other cognitive deficits (e.g., latent construct of executive function) were hypothesized to be less likely to distinguish between those older adults with MDD from those with MDD and preclinical AD.

As predicted, tests of long-term memory (assessed as both a latent construct in a SEM and as individual tests in logistic regression analyses) were associated with the development of AD over time to a greater extent than neuropsychological tests associated with executive function and covariates including age. This was the first study, to our knowledge, to assess

the relationship between domains of cognitive functioning and AD using this theoretical model.

Our findings are consistent with other research in the field on depressed elders (Visser et al., 2000) and the cognitive functions known to be first impaired in AD, showing that episodic memory impairment is associated with preclinical AD. The formation of long-term memory is dependent on medial temporal lobe structures, which consist of the hippocampus, the entorhinal, perirhinal, and parahippocampal cortices. Atrophy of the entorhinal cortex and hippocampus has significant prognostic value in detecting subjects with progressive MCI (Tapiola et al., 2008). Thus, detection of long-term memory deficits, episodic memory in particular, is critical for the early identification of AD among depressed patients.

Though our results were consistent with our hypothesis, we were also aware that individuals in the preclinical AD phase would likely score lower across most neuropsychological tests. Whereas our model of long-term memory predicting AD was consistent with our results, we also found impaired executive functioning was associated with AD, but to a lesser extent. There is evidence suggesting AD is a somewhat heterogeneous disorder which may imply multiple causal pathways such that some AD patients will have disproportionate executive function impairment (Johnson, Head, Kim, Starr, & Cotman, 1999). Thus, some depressed older adults with preclinical AD manifest degraded performance on tests other than long-term memory. In addition, some AD patients present with mixed pathology (e.g., preclinical AD and neurological damage related to vascular disease or stroke) in which tests of executive function and long-term memory are impacted (Bastos-Leite et al., 2007).

Our theoretical model was not directly clinically applicable, and thus, we performed logistic regression analyses to determine the individual neuropsychological tests that were able to predict conversion AD. One major clinical implication of this study is that patients presenting with acute depression who also present with deficits in long-term memory should be considered at risk for conversion to AD. Examination of the loadings on the latent variables and then follow-up analyses with logistic regression showed that tests of episodic memory, in particular the Wechsler Memory Scale-Revised (WMS-R) Logical Memory Delayed Recall subtest and the CERAD Word List Learning Delayed Recall subtest had the largest standardized regression coefficients. Patients who converted to AD scored eight points lower (about 1 *SD*) on Logical Memory and almost 1 *SD* lower on Word List Learning on average at baseline than patients who remained dementia-free. Means presented in Table 1 provide clinicians with raw scores by which to gauge the relative performance of their own depressed patients, keeping in mind the demographic characteristics of this sample.

It would be of great importance to replicate these findings in a less educated and more diverse population across different age groups, and the extent to which these findings are stable across different populations would be of great clinical relevance. Clearly, establishing normative data for older patients with MDD is necessary (as opposed to healthy older adults for whom normative data are available), because older patients with MDD (who do not convert to AD) will likely demonstrate decrements on most measures of memory and concentration during the acute phase of the depressive episode. Indeed, in a study based on these same data (Lee et al., 2007), about 52% of depressed patients had remitted from their depression 1 year later; among those who had remitted, 55% were classified as having some cognitive impairment at baseline (1.5 *SD* below mean levels on one or more neurocognitive tests).

Surprisingly, a test of episodic memory with the next highest loading on the long-term memory latent variable, CERAD Constructional Praxis Delayed Recall, was not

significantly related to AD in logistic regression analyses. Though visual episodic memory has been shown to be impaired in other studies of preclinical AD (Guarch, Marcos, Salamero, Gasto, & Blesa, 2008), we found only tests of verbal episodic memory to be associated with AD. One possibility to account for this finding is that depressed patients in the current study may have performed poorly on this subtest, which has a large motor component and requires sustained effort. These additional skills are not required on the verbal episodic memory tests in our battery and are often impaired among depressed patients in general (Austin et al., 2001). Thus, it is possible that the performance of the depressed patients in general was too similar to the preclinical AD patients' to detect differences on this subtest.

Another possibility that must be considered to account for the greater sensitivity of some tests is that the properties of the tests themselves may have impacted our findings. Specifically, changes in cognitive function should appear earlier for tests without ceiling effects and with high reliability (Chapman & Chapman, 1973). The MMSE is one test known to suffer from ceiling effects (Ihl, Frolich, Dierks, Martin, & Maurer, 1992), and the only tests in our battery that had significant negative skew (i.e., skewness value less than -2) were the MMSE subtests. Additionally, the MMSE attention indicator was composed of a single item, which may have reduced reliability of the variable. Indeed, this was the indicator with the smallest loading on the long-term memory latent variable. Further, our finding that long-term memory tests were associated with AD to a greater extent than executive function tests may have been an artifact of having more reliable measures. However, in review of the literature, there was no apparent superiority of the long-term memory tests. Although we cannot confirm the theory that long-term memory is initially affected more than executive function, importantly, we were able to identify at least two tests of episodic memory that may be useful in identifying preclinical AD.

Many factors contribute to the development of AD. In addition to examining the predictive value of neuropsychological tests, we also examined the influence of psychosocial variables. Consistent with other studies, advancing age was related to AD. It is important to note, however, that long-term memory tests predicted conversion to AD over and above the influence of age, and that the standardized regression coefficient of the Logical Memory test was greater than that of age. Interestingly, having *fewer* depressive symptoms at baseline was associated with greater likelihood of AD. This finding may be consistent with the prodrome hypothesis of MDD and AD, in which those individuals with late-onset MDD and a less severe depression course (i.e., fewer episodes and symptoms) may have developed mild depressive symptoms as a consequence of early neurological changes in preclinical AD. It may also be the case that individuals in the early stages of AD were beginning to experience cognitive deficits and developed mild depressive symptoms in reaction to early cognitive losses (Jorm, 2001).

LIMITATIONS

As with any study, there were several limitations to the present investigation. Our sample consisted mostly of highly educated, Caucasian participants. There is evidence to suggest that greater levels of education are associated with higher scores on the CERAD battery (Unverzagt et al., 1996). It would be important to determine if our results generalize to a less educated and more diverse population. In order for this study's findings to have practical implications, future research should examine neuropsychological predictors of AD among more diverse samples and strive to generate applicable norms and cut-scores across age groups. Clearly this would be a major undertaking.

We must also consider that treatment may have affected outcomes. Patients underwent naturalistic treatment for MDD, and another limitation is that we did not have current treatment data. However, 14 participants reported having received ECT in the past. There is some evidence to suggest that ECT impairs cognitive functioning, though cognitive deficits are not long-lasting (Devanand, Dwork, Hutchinson, Bolwig, & Sackeim, 1994). Importantly, in our sample there were no significant differences in global cognitive functioning at baseline or AD status at follow-up between those who had received ECT in the past and those who had not received ECT or between those who had taken antidepressant medication versus those who had not taken medication.

A priori power to detect effects was low for some analyses, particularly the hierarchical logistic regression analysis. However, we did find significant effects for a long-term memory test (WMS-R Logical Memory Delayed Recall) and several covariates, as discussed earlier. Nonetheless, we cannot rule out the possibility that we may have found an effect in the logistic regression analyses for more of the executive function tests had we been able to obtain data from more patients, and thus, increased our sample size.

Patients with missing data or those excluded due to inadequate followup time ($n = 28$) had fewer years of education and lower global cognitive functioning scores at baseline. These characteristics have been associated with greater risk for AD. Furthermore, those who developed AD were significantly older than those who did not. Not only must age be considered as a potential confound in studies of conversion to AD, but given adequate followup time, which varied in the current study from 2.5 to 12 years, we may be able to identify more participants who develop AD. Thus, we may have been more likely to detect AD among some of the patients who were excluded or followed-up for fewer years, which reduces diagnostic accuracy and restricts the generalizability of our results to this population.

CONCLUSIONS

Our results have implications for early recognition and treatment of AD among depressed older adults. Clinicians often face a diagnostic quandary when an older depressed patient presents with cognitive impairment. In order to distinguish preclinical AD from reversible cognitive impairment seen in MDD, clinicians may consider administering tests of episodic memory that indicate long-term memory impairment, in particular, the WMS-R Logical Memory Delayed Recall subtest and the CERAD Word List Learning delayed recall subtest. At least 1 *SD* below the mean on these tests in relation to the scores derived for the population based on age and education should alert the clinician to the possibility of preclinical AD, and subsequent testing should be conducted to gauge the patient's status. Future research should determine if those with preclinical AD and who have relative deficits on the identified tests show substantial improvement when the MDD remits or whether the scores continue to show deficits after remission.

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FIGURE 1.

Results from theoretical structural equation model: Association of long-term memory and executive function domains at baseline to Alzheimer's disease status at follow-up.

Table 1

Key variables at baseline reported by Alzheimer's disease status as assessed at follow-up

Variable	n	AD (n = 15)	No dementia (n = 105)	Total (N = 120)	F or ²	p-Value
Demographics						
Sex (Female)	120	11 (73.3%)	66 (62.9%)	77 (64.2%)	$\chi^2(1, N = 120) = 0.63$	.429
Age	120	74.2 (8.0)	67.4 (6.1)	68.2 (6.7)	$F(1, 118) = 15.30$	<.001
Race	120				$\chi^2(3, N = 120) = 3.87$	.276
Asian		0 (0%)	2 (1.9%)	2 (1.7%)		
African American		3 (20.0%)	7 (6.7%)	10 (8.3%)		
Caucasian		12 (80.0%)	91 (86.7%)	103 (85.8%)		
Other		0 (0%)	5 (4.8%)	5 (4.2%)		
Years of education	120	13.8 (3.9)	14.2 (2.5)	14.2 (2.7)	$F(1, 118) = 0.33$	.567
Health Problems (Yes)						
Asthma	120	0 (0%)	7 (6.7%)	7 (5.8%)	$\chi^2(1, N = 120) = 1.06$	.303
Diabetes	120	1 (6.7%)	8 (7.6%)	9 (7.5%)	$\chi^2(1, N = 120) = 0.02$	.896
Heart trouble	120	3 (20.0%)	19 (18.1%)	22 (18.3%)	$\chi^2(1, N = 120) = 0.03$	.858
Hypertension	120	7 (46.7%)	45 (42.9%)	52 (43.3%)	$\chi^2(1, N = 120) = 0.08$	.781
Arthritis	119	9 (64.3%)	57 (54.3%)	66 (55.5%)	$\chi^2(1, N = 120) = 0.50$	.479
Stroke	120	1 (6.7%)	6 (5.7%)	7 (5.8%)	$\chi^2(1, N = 120) = 0.02$	.883
Cancer	120	0 (0.0%)	5 (4.8%)	5 (4.2%)	$\chi^2(1, N = 120) = 0.75$	.388
Emphysema	120	0 (0.0%)	8 (7.6%)	8 (6.7%)	$\chi^2(1, N = 120) = 1.224$	.268
Ulcers	120	1 (6.7%)	6 (5.7%)	7 (5.8%)	$\chi^2(1, N = 120) = 0.02$	.883
Hardening of arteries	116	1 (1.1%)	15 (14.6%)	16 (13.8%)	$\chi^2(1, N = 120) = 0.46$	.498
Depression Severity						
Age at first episode	119	53.4 (24.4)	42.7 (19.1)	44.0 (20.1)	$F(1117) = 3.83$	.053
Number of episodes	118	3.2 (2.4)	7.5 (16.3)	7.0 (15.4)	$F(1116) = 1.05$	.308
Number of DSM-IV symptoms	120	5.5 (2.6)	6.3 (2.4)	6.2 (2.4)	$F(1118) = 1.58$	.211
Neuropsychological Tests						
WMS-R ^a Logical Memory Delayed Recall	118	12.9 (9.5)	21.1 (9.0)	20.0 (9.4)	$F(1116) = 10.56$	.002
CERAD ^b Word List Learning Delayed Recall	120	4.5 (3.0)	6.3 (2.1)	6.1 (2.3)	$F(1118) = 9.13$	.003

Variable	n	AD (n = 15)	No dementia (n = 105)	Total (N = 120)	F or χ^2	p-Value
CERAD ^b Constructional Praxis Delayed Recall	120	6.0 (3.0)	8.1 (2.4)	7.9 (2.6)	$F(1, 118) = 9.66$	.002
MMSE ^c Delayed Recall Items	120	2.0 (1.1)	2.7 (0.6)	2.6 (0.7)	$F(1, 118) = 15.37$	<.001
CERAD ^b Category Fluency	120	14.3 (7.1)	16.1 (4.9)	15.9 (5.3)	$F(1, 118) = 1.50$	.223
CERAD ^b Boston Naming Test	120	13.5 (1.2)	13.9 (1.5)	13.9 (1.5)	$F(1, 118) = 0.83$	.363
MMSE ^c Orientation Items	120	8.4 (1.8)	9.5 (0.7)	9.4 (1.0)	$F(1, 118) = 18.99$	<.001
Benton Visual Retention Test	118	4.1 (2.3)	5.5 (2.2)	5.3 (2.3)	$F(1, 116) = 4.55$	.035
Symbol Digit Modalities Test	116	30.0 (14.5)	36.7 (10.9)	35.9 (11.5)	$F(1, 114) = 4.23$	.042
Trail Making Test Part B – Part A	113	98.0 (66.7)	89.2 (65.2)	90.1 (65.1)	$F(1, 111) = 0.20$	.659
WAIS-R ^d Digit Span Backward	103	5.7 (2.0)	6.9 (2.4)	6.8 (2.4)	$F(1, 101) = 3.10$	.081
Ascending Digit Span	103	6.5 (3.3)	8.3 (2.6)	8.1 (2.7)	$F(1, 101) = 5.37$	.023
MMSE ^c Attention Item	120	4.5 (1.1)	4.8 (0.7)	4.8 (0.7)	$F(1, 118) = 2.85$	.094

^aWechsler Memory Scale-Revised.

^bConsortium to establish a registry for Alzheimer's disease.

^cMini-Mental Status Examination.

^dWechsler Adult Intelligence Scale-Revised.

Table 2

Number of new Alzheimer's disease cases at each year of follow-up

	Frequency	Cumulative frequency
Year 2–3	1	1
Year 3–4	3	4
Year 4–5	2	6
Year 5–6	1	7
Year 6–7	1	8
Year 7–8	1	9
Year 8–9	3	12
Year 9–10	1	13
Year 10–11	0	13
Year 11–12	1	14
Year 12–13	1	15

Table 3

Structural equation model predicting long-term memory function would be most predictive of conversion to AD compared to executive function

Parameter	Standardized estimate	Standard error	p-Value
Long-term Memory Loadings			<.001
WMS-R ^a Logical Memory Delayed Recall	0.762	0.046	<.001
CERAD ^b Word List Learning Delayed Recall	0.684	0.055	<.001
CERAD ^b Constructional Praxis Delayed Recall	0.739	0.047	<.001
MMSE ^c Delayed Recall Items	0.650	0.059	<.001
CERAD ^b Category Fluency	0.681	0.055	<.001
CERAD ^b Boston Naming Test	0.556	0.069	<.001
MMSE ^c Orientation Items	0.553	0.069	<.001
Executive Function Loadings			
Benton Visual Retention Test	0.813	0.039	<.001
Trail Making Test Part B – Part A	–0.753	0.051	<.001
Symbol Digit Modalities Test	0.810	0.039	<.001
WAIS-R ^d Digit Span Backward	0.614	0.066	<.001
Ascending Digit Span	0.644	0.063	<.001
MMSE ^c Attention Item	0.351	0.086	<.001
Long-term Memory Function on Alzheimer's Disease	–0.366	0.087	<.001
Executive Function on Alzheimer's Disease	–0.248	0.093	0.012
Correlation of Long-term Memory and Executive Function	0.934	0.035	<.001
Residual Variances			
WMS-R ^a Logical Memory Delayed Recall	0.420	0.070	<.001
CERAD ^b Word List Learning Delayed Recall	0.532	0.075	<.001
CERAD ^b Constructional Praxis Delayed Recall	0.454	0.070	<.001
MMSE ^c Delayed Recall Items	0.577	0.076	<.001
CERAD ^b Category Fluency	0.537	0.075	<.001
CERAD ^b Boston Naming Test	0.691	0.076	<.001
MMSE ^c Orientation Items	0.694	0.076	<.001
Benton Visual Retention Test	0.339	0.063	<.001
Symbol Digit Modalities Test	0.343	0.063	<.001
Trail Making Test Part B – Part A	0.433	0.077	<.001
WAIS-R ^d Digit Span Backward	0.623	0.081	<.001
Ascending Digit Span	0.585	0.081	<.001
MMSE ^c Attention Item	0.877	0.060	<.001

^aWechsler Memory Scale-Revised.

^bConsortium to establish a registry for Alzheimer's disease.

^cMini-Mental Status Examination.

^dWechsler Adult Intelligence Scale-Revised.

Table 4

Correlations among neuropsychological tests at baseline

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. WMS-R ^a Logical Memory Delayed Recall	1	.573**	.588**	.441**	.506**	.390**	.341**	.518**	.544**	-.490**	.456**	.448**	.163
2. CERAD ^b Word List Learning Delayed Recall	.573**	1	.483**	.528**	.383**	.410**	.423**	.398**	.552**	-.319*	.455**	.378**	.190*
3. CERAD ^b Constructional Praxis Delayed Recall	.588**	.483**	1	.486**	.453**	.327**	.473**	.629**	.496**	-.407**	.407**	.401**	.301*
4. MMSE ^c Delayed Recall Items	.441**	.528**	.486**	1	.455**	.278**	.455**	.431**	.468**	-.261*	.337**	.388**	.219*
5. CERAD ^b Category Fluency	.506**	.383**	.453**	.455**	1	.464**	.329**	.549**	.616**	-.485**	.373**	.493**	.153**
6. CERAD ^b Boston Naming Test	.390**	.410**	.327**	.278**	.464**	1	.283**	.458**	.478**	-.406**	.369**	.361**	.137
7. MMSE ^c Orientation Items	.341**	.423**	.473**	.445**	.329**	.283*	1	.355**	.351**	-.233	.303*	.275**	.313**
8. Benton Visual Retention Test	.518**	.398**	.629**	.431**	.549**	.458**	.355**	1	.641**	-.584**	.462**	.543**	.315*
9. Symbol Digit Modalities Test	.544**	.552**	.496**	.468**	.616**	.478**	.351**	.641**	1	-.567**	.431**	.497**	.212*
10. Trail Making Test Part B – Part A	-.490**	-.319*	-.407**	-.261*	-.485**	-.406**	-.233*	-.584**	-.567**	1	-.368**	-.330*	-.239**
11. WAIS-R ^d Digit Span Backward	.456**	.455**	.407**	.337**	.373**	.369**	.303*	.462**	.431**	-.368**	1	.524**	.353**
12. Ascending Digit Span	.448**	.378**	.401**	.388**	.493**	.361**	.275*	.543**	.497**	-.330*	.524**	1	.191
13. MMSE ^c Attention Item	.163	.190*	.301*	.219*	.153	.137	.313**	.315*	.212*	-.239*	.353**	.191	1

^aWechsler Memory Scale-Revised.

^bConsortium to establish a registry for Alzheimer's disease.

^cMini-Mental Status Examination.

^dWechsler Adult Intelligence Scale-Revised.

***Not Significant at the .01 level;

* Significant at the .05 level.

Table 5
Hierarchical logistic regression analysis predicting Alzheimer's disease status at follow-up

	Variable	b	Standard error	Wald	df	P	Odds ratio
Step 1 $\chi^2(7, N=108) = 20.97, p = .004$ 92.6 PAC ^d	Sex	0.883	0.886	0.993	1	.319	2.418
	Age	0.178	0.064	7.654	1	.006	1.195
	Race	-0.311	1.074	0.084	1	.772	0.733
	Education	0.278	0.162	2.940	1	.086	1.321
	Age of depression onset	0.021	0.026	0.679	1	.410	1.021
	Number of depressive episodes	-0.021	0.055	0.146	1	.703	0.979
Step 2 $\chi^2(10, N=108) = 30.778$ $p = .001$. 93.5 PAC ^d	Number of current depressive symptoms	-0.436	0.177	6.028	1	.014	0.647
	Sex	0.362	0.993	0.133	1	.715	1.437
	Age	0.167	0.079	4.509	1	.034	1.182
	Race	0.844	1.367	0.381	1	.537	2.325
	Education	0.534	.225	5.615	1	.018	1.706
	Age of depression onset	0.008	0.029	0.080	1	.777	1.008
Step 3 $\chi^2(13, N=108) = 33.019$ $p = .002$. 92.6 PAC ^d	Number of depressive episodes	-0.028	0.087	0.106	1	.744	0.972
	Number of current depressive symptoms	-0.715	0.242	8.728	1	.003	0.489
	WMS-R ^b Logical Memory Delayed Recall	-0.216	0.104	4.278	1	.039	0.806
	CERAD ^c Word List Learning Delayed Recall	0.163	0.251	0.422	1	.516	1.177
	CERAD ^c Constructional Praxis Delayed Recall	-0.047	0.254	0.034	1	.853	0.954
	Sex	0.130	1.033	0.016	1	.900	1.139
	Age	0.206	0.102	4.088	1	.043	1.229
	Race	1.195	1.539	0.603	1	.437	3.304
	Education	0.792	0.345	5.269	1	.022	2.209
	Age of depression onset	0.013	0.034	0.150	1	.698	1.013
	Number of depressive episodes	-0.038	0.119	0.103	1	.748	0.962
	Number of current depressive symptoms	-0.767	0.274	7.816	1	.005	0.464
	WMS-R ^b Logical Memory Delayed Recall	-0.225	0.118	3.650	1	.056	0.798
	CERAD ^c Word List Learning Delayed Recall	0.174	0.275	0.397	1	.528	1.190
	CERAD ^c Constructional Praxis Delayed Recall	-0.089	0.257	0.121	1	.728	.915

Variable	<i>b</i>	Standard error	Wald	df	<i>P</i>	Odds ratio
Benton Visual Retention Test	−0.314	0.382	0.675	1	.411	0.730
Symbol Digit Modalities Test	0.068	0.087	0.618	1	.432	1.070
Trail Making Test Part B – Part A	0.008	0.009	0.833	1	.361	1.009

^aPAC = percentage accuracy in classification.

^bWechsler Memory Scale-Revised.

^cConsortium to establish a registry for Alzheimer’s disease.

Table 6

Calculation of standardized regression coefficients predicting Alzheimer's disease status at follow-up

Variable	s_x	Full Model ^d		Separate Models		
		b		b	R	$S_{Y_{pred}}$
WMS-R ^b Logical Memory Delayed Recall	9.423	-0.225	-0.443	-0.098	.324	0.923
CERAD ^c Word List Learning Delayed Recall	2.313	0.174	0.084	-0.340	.326	0.787
CERAD ^c Constructional Praxis Delayed Recall	2.564	-0.089	-0.048	-0.289	.284	0.741
Benton Visual Retention Test	2.269	-0.314	-0.149	-0.255	.194	0.579
Symbol Digit Modalities Test	11.515	0.068	0.164	-0.052	.232	0.599
Trail Making Test Part B – Part A	65.119	0.008	0.109	0.002	.039	0.130

Note: s_x = Standard deviation of predictor variable; b = Unstandardized regression coefficient; = Standardized regression coefficient (calculated); R = Square root of explained variance; $S_{Y_{pred}}$ = Estimated standard deviation of predicted values of logit(Y).

^aFull Model with all tests and control variables included as covariates: $R = .646$ and $S_{Y_{pred}} = 3.09$.

^bWechsler Memory Scale-Revised.

^cConsortium to establish a registry for Alzheimer's disease.