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Clinical predictors of progression to Alzheimer disease in amnestic mild cognitive impairment

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ABSTRACT Objective: To investigate the neurocognitive measures that best predict progression from amnestic mild cognitive impairment (aMCI) to Alzheimer disease (AD). **Methods:** We evaluated 539 participants with aMCI from the Alzheimer's Disease Cooperative Study clinical drug trial of donepezil, vitamin E, or placebo. During the study period of 36 months, 212 aMCI participants progressed to AD. Using progression from aMCI to AD within 36 months as the dependent variable, a generalized linear model was fit to the data using the least absolute shrinkage and selection operator. Independent variables included in this analysis were age, sex, education, APOE-e4 (APOE4) status, family history of dementia, Mini-Mental State Examination score, Digits Backwards (Wechsler Memory Scale), Maze Time and Errors, Number Cancellation, Delayed Recall of Alzheimer's Disease Assessment Scale Word List, New York University Paragraph Recall Test (Immediate and Delayed), Boston Naming Test, Category Fluency, Clock Drawing Test, and the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-cog). **Results:** The model that best predicted progression from aMCI to AD over 36 months included APOE4 status, the Symbol Digit Modalities Test, Delayed 10-Word List Recall, New York University Paragraph Recall Test (Delayed), and the ADAS-cog total score. When APOE4 was removed from the analysis the resulting model had a similar estimated predictive accuracy as the full model. As determined by cross-validation, the estimated predictive accuracy of the final model was 80%. **Conclusion:** Progression from amnestic mild cognitive impairment to Alzheimer disease in this cohort was best determined by combining four common, easily administered, cognitive measures.
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The neurocognitive deficits that best define the natural history of mild cognitive impairment (MCI) in predicting progression to Alzheimer disease (AD) are poorly understood. Studies predicting progression from MCI to AD have generally focused on only one or two of the following three risk categories: 1) demographic factors such as age, sex, and education; 2) neurocognitive performance; or 3) biologic factors, such as the presence of the apolipoprotein e4 allele (APOE4). Another limitation to many previous studies is the heterogeneity in how the predementia diagnosis is defined and not using formal criteria for determining MCI.[1-6] Furthermore, studies frequently ignore or control for risk factors such as age, sex, education, family history, or APOE status rather than including them in the predictive model.[1,6-10] In addition, some studies that have used demographics, biologic risk, and neurocognitive measures in their predictive models are restricted by sample size[11-15] or demographically narrow cohorts.[10,16] For all these reasons, it has been difficult to develop stable, generalizable, and pragmatic predictive models of progression to AD.

In this report, we investigate the neurocognitive measures that best predict progression from amnestic MCI (aMCI) to AD in a cohort of participants from the Alzheimer's Disease Cooperative Study (ADCS) MCI treatment trial.[17] We incorporate known demographic and genetic risk factors with common neurocognitive test measures to develop a practical formula for calculating the probability that an individual will progress to AD in a 3-year period based on the progression rates in this cohort.

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METHODS

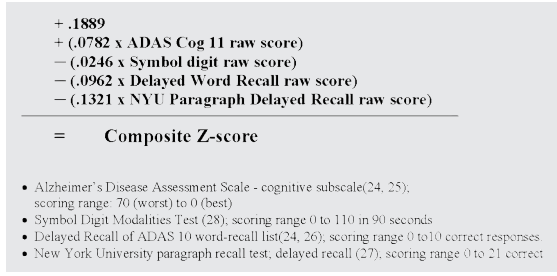
Study design. The ADCS conducted a 36-month randomized drug trial consisting of three parallel drug arms: donepezil (10 mg), vitamin E (2,000 IU), and placebo. All groups also received a multivitamin. A total of 2,264 participants were screened for participation, 790 aMCI participants were randomized, and 769 underwent baseline evaluations. The study was conducted between March 1999 and January 2004 with participant recruitment at 69 ADCS sites in the United States and Canada.[18] For this trial, an advertising campaign targeting elderly persons in the cities of the ADCS participating centers as well as local site recruitment procedures were used to procure the participants. For inclusion, participants needed to meet criteria for amnestic MCI of a degenerative nature,[19,20] have sufficiently preserved global cognitive and functional performance that would not meet National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) dementia criteria,[21] have a memory complaint corroborated by an informant, have a Wechsler Memory Scale–Revised Logical Memory II Cutoff score approximately 1.5 to 2 SDs below the education adjusted norm (delayed recall of one paragraph),[22] be 55 to 90 years of age inclusive, and have a Clinical Dementia Rating (CDR) score of 0.5 and a Mini-Mental State Examination (MMSE) score between 24 and 30 (inclusive). Participants were excluded who had a history of significant cerebral vascular disease based on a modified Hachinski score >4; depression based on a Hamilton Depression Rating Scale score >12; CNS infarct; infection or focal lesions of clinical significance on CT or MRI scan; medical diseases or psychiatric disorders that could interfere with study participation; were pregnant, lactating, or of childbearing potential; or taking vitamins or other supplements. Details of the study design were previously presented.[17]

Outcome measures. The primary endpoint in this longitudinal drug trial was the development of possible or probable AD according to NINCDS-ADRDA criteria.[21] When the clinical diagnosis of AD was made, all cognitive and functional data were sent to the ADCS Coordinating Center and forwarded to a five-member central review committee for a consensus of the diagnosis.

Clinical variables. The participants were assessed at baseline and with 3 years of follow-up. Clinical evaluations were performed every 3 months for the first 6 months and then every 6 months thereafter. A variety of neurocognitive measures were collected. These included the Folstein Mini-Mental State Examination,[23] Alzheimer's Disease Assessment Scale (ADAS)–Cognitive subscale (ADAS-cog),[24,25] Delayed Recall of the ADAS 10-Word List Recall,[24,26] the New York University (NYU) Paragraph Recall Test (Immediate and Delayed),[27] the Symbol Digit Modalities Test,[28] Category Fluency Test,[29] a number cancellation test,[30] the Boston Naming Test (10-picture version),[31] the Digits Backwards Test,[32] clock drawing, and a maze tracing task.[30] In addition to neurocognitive evaluations, all participants received baseline and follow-up assessments of overall dementia severity and functional status with the Clinical Dementia Rating (CDR),[33] ADCS MCI-Activities of Daily Living (ADL) Scale,[34] and the Global Deterioration Scale (GDS).[35]

Conduct of the study. The study was conducted according to Good Clinical Practice, the Declaration of Helsinki, and U.S. 21 CFR Part 50-Protection of Human Subjects and Part 56–Institutional Review Boards. Written informed consent for the study was obtained from all the participants and study partners before protocol-specific procedures, including cognitive testing, were performed.

Figure 1 Formula for calculating the composite *Z* score for the final predictive model including the Alzheimer's Disease Assessment Scale–Cognitive subscale, Symbol Digit Modalities Test, Delayed Word List Recall, and New York University (NYU) Paragraph Recall Test. The resulting *Z* score can be used to predict progression from aMCI to AD.

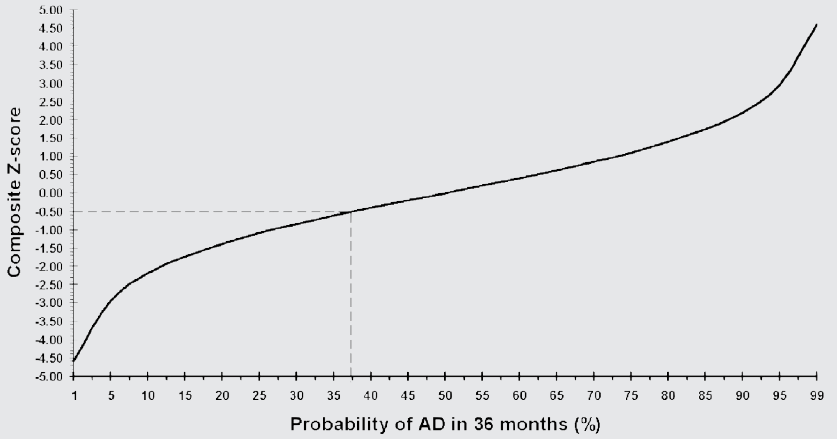


Statistics. Analysis was only performed on participants who met criteria for AD within 36 months or completed a 36-month visit. Using progression from aMCI to AD within 36 months as the dependent variable, a generalized linear model (GLM) was fit to the data using the least absolute shrinkage and selection operator (LASSO).[36] LASSO uses a variant of forward selection that shrinks the individual regression coefficients toward zero. Shrinkage such as this can improve the predictive accuracy of fitted models. Depending on the fit and estimated accuracy, some covariates may not appear in the final model selected by LASSO, and the regression coefficients corresponding to these variables can be said to have been "shrunk to 0," leading to parsimonious and interpretable models. Predictive accuracy was assessed by 10-fold cross-validation. The independent variables included in the analysis were age, sex, years of education, APOE4 status, family history of dementia, and all baseline neurocognitive measures. Overall dementia severity and functional status, as measured by the CDR, ADL Scale, and GSD, were not included in this analysis. To assess the impact of knowing APOE4 status on the predictive accuracy of the model the regression was run once including APOE4 status as a predictor and a second time not including APOE4 status as a predictor. To further focus on domain-specific cognitive instruments, a model was analyzed using age, sex, education, family history of dementia, and only domain-specific cognitive measure, removing the ADAS-cog and the MMSE as independent variables. Treatment arms were included as a factor in each model to statistically control for drug effects over the 3-year treatment trial.

Using the resulting estimated regression coefficients, a composite score, which will be called a *Z* score, was calculated. The *Z* score was formulated by multiplying the individual regression coefficients of variables in the optimal predictive model by the value of the respective variable test score, and summing these products (figure 1). From this *Z* score, the probability of progression from aMCI to AD over 36 months can be calculated using the following formula: Probability of progression to AD = $e^Z/(1 + e^Z)$, where e is the natural log constant 2.71828.

This formula is graphically represented in figure 2 with *Z* scores on the *y* axis and probability of converting to AD in 36 months on the *x* axis. An individual's neurocognitive test scores

Figure 2 Graph representing the logarithmic conversion formula for the probability of progression from amnestic mild cognitive impairment to Alzheimer disease over 36 months. An individual's *Z* score can be applied to this figure to determine the corresponding probability on the *x* axis. The dashed line indicates the mean composite *Z* score and a priori probability of progression for this cohort over 36 months.



from the measures in our final predictive model can be combined to calculate a composite *Z* score for that individual using the formula provided in figure 1. This *Z* score can then be used to calculate a probability of progression to AD over 36 months (in percentage) from the above log formula or approximated by using the provided look-up table (table 1) generated from this predictive model.

Table 1 Probability of progression from amnestic mild cognitive impairment to AD in 36 months

Composite *Z* score	Probability of AD in 36 mo (%)
−4.595	1
−2.944	5
−2.197	10
−1.735	15
−1.386	20
−1.099	25
−0.847	30
−0.619	35
−0.405	40
−0.201	45
0.000	50
0.201	55
0.405	60
0.619	65
0.847	70
1.099	75
1.386	80
1.735	85
2.197	90
2.944	95
4.595	99

AD = Alzheimer disease.

RESULTS

Treatment trial outcome measures. Of the 769 participants baselined, 539 participants reached either study end or the primary endpoint of progression to AD; 212 of these progressed to AD, whereas the remaining 327 did not meet criteria for AD at 36 months.[17] Of those participants who did not convert to AD by the end of the 3-year study, two progressed to a non-AD dementia, one with mixed dementia and one with primary progressive aphasia. These two participants were not included in the current analyses of 539 aMCI participants. Over the course of the 36-month study, the overall rate of progression from MCI to AD was 16% per year. As previously reported, there were no differences in progression to AD between treatment arms at 36 months.[17] Baseline demographic and cohort measures are shown in table 2.

Outcomes and adverse events. A total of 230 participants discontinued participation during the double-blind treatment trial: donepezil (n = 92), vitamin E (n = 72), and placebo (n = 66) ($p = 0.896$). No significant differences overall were observed for the demographic and neurocognitive measures between the participants who dropped out of the trial before progression to AD and those who completed the trial or progressed to AD.[17] However, a contingency table analysis of the number of withdrawn participants categorized by treatment and period of withdrawal indicated a trend toward more early dropouts (at the 3- and 6-month visits) in the donepezil group than in the placebo group ($p = 0.069$). Further detail of dropout and adverse event analyses were presented in the primary treatment trial publication.[17]

Predictive model outcomes. When APOE status was included in the analysis, the model most predictive of progression from aMCI to AD over 36 months included APOE4 allele status, the Symbol Digit Modalities Test, Delayed 10-Word List Recall, NYU Delayed Paragraph Recall Test, and the ADAS-cog total score. The estimated predictive accuracy of this model is 81% (95% CI: 0.79 to 0.83) as determined by 10-fold cross-validation.

When APOE status was not included in the analysis, the model most predictive of progression to AD from MCI consisted of the same four neurocognitive measures as the model with APOE. This model provided a similar predictive accuracy of 80% (95% CI: 0.78 to 0.82). APOE

Table 2 Demographics with baseline global, functional, and cognitive measures

	Progressors	Nonprogressors	*p* Values
No. of participants	212	327	
Age, y	74.87 ± 6.64	71.52 ± 7.41	<0.001*
Sex (% female)	46.7	40.67	0.182
Education, y	14.47 ± 3.10	14.97 ± 2.84	0.04*
ApoE 4 status (% positive)	161 (75.94)	143 (43.73)	<0.001*
APOE-e2,e2 (%)	0	0	NA
APOE-e2,e3 (%)	8 (3.77)	21 (6.42)	0.241†
APOE-e3,e3 (%)	43 (20.28)	163 (49.85)	<0.001*†
APOE-e2,e4 (%)	9 (4.25)	8 (2.45)	0.313†
APOE-e3,e4 (%)	123 (58.0)	108 (33.03)	<0.001*†
APOE-e4,e4 (%)	29 (13.6)	27 (8.26)	0.059†
CDR-SB	2.20 ± 0.79	1.60 ± 0.71	<0.001*
GDS	2.87 ± 0.61	2.62 ± 0.56	<0.001*
ADL	44.04 ± 5.47	47.16 ± 3.82	<0.001*
Symbol Digit Modalities	25.86 ± 9.73	35.69 ± 9.97	<0.001*
NYU Delayed Paragraph Recall Test	1.84 ± 1.87	4.58 ± 2.84	<0.001*
ADAS-cog total score	13.97 ± 4.07	9.45 ± 3.65	<0.001*
Delayed 10-Word List Recall	2.34 ± 1.86	4.52 ± 2.10	<0.001*

*Significant.
†Tested at the 0.01 level to correct for multiple comparisons.
CDR-SB = Clinical Diagnostic Rating Scale sum of boxes; GDS = Global Deterioration Scale; ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; NYU = New York University; ADAS-cog = Alzheimer's Disease Assessment Scale–Cognitive subscale.

status was associated, using Spearman's rank correlations, with all variables in the final model: Symbol Digit Modalities ($r = -0.137$ $p = 0.002$) Delayed 10-Word List Recall ($r = -0.235$, $p < 0.001$), NYU Delayed Paragraph Recall Test ($r = -0.251$, $p < 0.001$), ADAS-cog total score ($r = 0.220$, $p < 0.001$). Univariate predictive accuracies are given in table 3, with a comparison of raw baseline scores between progressors and nonprogressors shown in the table 2.

Given that the predictive accuracy of the primary model was similar to the model with APOE status removed, the composite *Z* score calculation presented in figure 1 is based on the four-variable predictive model that does not include APOE status. Based on this model, the range of composite *Z* scores for this cohort was −3.08 (4% probability of progression) to 1.83 (86%) with a mean of −0.54 ± 0.96 (ranging from 18% to 60%). *Z* scores for progressors were higher than *Z* scores for nonprogressors ($p < 0.001$).

Table 3 Univariate predictive accuracies within the full regression model

Final model variables	Univariate estimated predictive accuracy (%)	95% CIs
APOE-e4 status	64.1	0.641–0.655
Symbol Digit Modalities Test	70.7	0.699–0.717
NYU Delayed Paragraph Recall Test	73.2	0.718–0.739
ADAS-cog total score	73.7	0.73–0.747
Delayed 10-Word List Recall	73.5	0.73–0.744

NYU = New York University; ADAS-cog = Alzheimer's Disease Assessment Scale–Cognitive subscale.

The GLM that included only domain-specific cognitive instruments and demographic features resulted in a final predictive model that included the Symbol Digit Modalities Test, Delayed 10-Word List Recall, and NYU Delayed Paragraph Recall Test. This model provided a predictive accuracy of progression to AD of 76% (95% CI: 0.75 to 0.77). Nonoverlapping CIs for predictive accuracies indicate that this model is significantly different from the full model. A *Z* score for this model can be calculated using the following formula: 1.7467 − (0.0336 x Symbol Digit raw score) − (0.1764 x Delayed 10-Word List Recall raw score) − (0.1634 x NYU Paragraph Delayed Recall Test raw score) = *Z* score.

This score can also be applied to table 1 or figure 2 to determine an approximate probability of pro-

gression, or an exact probability score can be calculated by using the probability of progression to AD log formula provided in the Methods section.

DISCUSSION Progression from aMCI to AD in this cohort was best predicted by combining APOE status and four common, easily administered, neurocognitive measures. Despite APOE status being regarded as a strong predictor of progression from MCI to AD, removing it as a variable in the regression model resulted in a model with similar predictive accuracy. Yet, APOE4 status did appear to be a more predictive risk factor than family history, age, sex, or education. For independent cognitive domain measures, episodic memory (Delayed 10-Word List Recall and NYU Delayed Paragraph Recall Test) and executive functioning (Symbol Digit Modalities Test) were more important predictors of progression than were other measures of cognitive abilities. The ADAS-cog, a composite measure of global cognition, had one of the highest univariate predictive accuracies. Using the four common neurocognitive tests presented here in our predictive model, we developed a simple composite scoring calculation and probability table for progression to AD over 36 months. This is a practical tool that may be useful in assisting in short-term clinical prognostication and design of preventive clinical drug trials in AD.

Our results regarding neurocognitive domains that are most predictive of progression to AD are consistent with those in previous literature. Delayed episodic recall and executive function were most predictive of progression to AD in our model as demonstrated by the Delayed 10-Word List Recall, delayed verbal recall of the NYU Paragraph Recall Test, and Symbol Digit Modalities Test. Episodic memory has been reported to be significantly predictive of progression from MCI to AD.[2,9,16,37,38] This seems intuitive given that episodic memory problems are prominent in early AD.[39] Tasks that require executive functioning, which includes planning, inhibition, organization, and initiation, have been demonstrated to be predictive of progression as well.[7,16,40] Executive dysfunction is also known to be a prominent feature in early AD.[41] It must be noted that our cohort was selected from MCI participants with prominent episodic memory and logical memory deficits. Therefore, our findings may not hold true for those with single-domain nonmemory MCI.[17]

Age, level of education, and sex were not significant predictors of progression from MCI to AD in our final model. Because age is one of the most salient risk factors for the development of AD,[42] we anticipated that it would be an important predictor of progression to AD in our cohort. However, despite a significant age difference between progressors and nonprogressors (table 2), age was not a predictor in our final model. There are conflicting reports in the literature regarding age as a risk factor for progression from MCI to AD.[9,43-45] Despite age being a predictor of incident MCI[44] and incident AD,[42] it may not significantly influence the duration of MCI prior to progression to AD. In other words, it may take the same amount of time to progress whether the individual is 55 years old or 90 years old. Alternatively, the age range in our cohort may have been too narrow to allow statistical power to detect an association between age and progression to AD. Likewise, education had a significantly restricted range in our cohort. Education[46,47] and sex[42,48] have been noted to be risk factors for AD, albeit somewhat more controversial. Even so, several previous studies have not found associations between sex[43-45] or education[9,43-45] and progression to AD from MCI.

It is not surprising that APOE4 status was found to be a predictor of progression from MCI to AD when it was included in the model, given its prominent role as a risk factor for AD. Although, as seen with our data on age, an association with AD does not always imply that the variable is a good predictor of progression to AD from MCI when given all the other factors. In fact, there is substantial conflict in the literature regarding APOE4 status as a predictor of progression from MCI to AD. Some studies support our finding,[12,14,49] but others do not show this relationship.[11,13,45] One study reports that when AD pathology is controlled for, the association between APOE4 and AD is attenuated, implying that this relationship is driven by a direct association between APOE4 and AD pathology.[50] Another study found that APOE4 was only a useful predictor of progression in 70 to 85 year olds while controlling for education, memory scores, and sex. Also, there was no additional predictive benefit to adding APOE4 to memory tests.[11] Likewise, it has been reported that APOE4 status is only useful if memory tests are included in the model.[15] Similarly, we found that APOE4 status does not improve our ability to predict progression from MCI to AD above that of memory and executive functioning tests by themselves. This is likely due to the association between APOE4 status and memory scores. With a strong association with AD pathology and memory scores, knowing APOE status may not be necessary for predicting progression to AD.

Our cohort was substantially larger than other cohorts reporting effects of APOE4 on prediction

of progression from MCI to AD. Due to high variability in progression rates, this added power may make a considerable difference in the ability to demonstrate APOE effects given the influence of the less common APOE4 homozygote subtype. Despite our cohort having no overall drug effects by study arm, the primary drug effect analysis did show slower progression rates in APOE4-positive participants on donepezil compared to those on placebo at 12, 24, and 36 months.[17] This treatment trial was not statistically powered to determine the effects of treatment in separate groups of APOE4 carriers and noncarriers. Even so, if a treatment effect exists in the APOE4 subgroup, it is possible that we are underestimating probabilities of progression in APOE4 carriers. However, our predictive model is less likely to be significantly driven by donepezil effects on the APOE4 subgroup because the drug arm was statistically controlled for in our analysis. In addition, the APOE genotype has been shown in this cohort to have differential effects by sex.[51] This leaves open the possibility that APOE genotype may have more predictive relevance in certain subgroups.

Limitations to our analyses should be noted. These predictive models were derived from a cohort of participants enrolled in a clinical drug trial. Although the population was acquired from 69 different regions around the United States and Canada, caution should be taken when generalizing our results. In this trial, exclusion and inclusion criteria were used to identify people with moderate degrees of aMCI who would have a high likelihood of converting during the 36-month trial. Therefore, generalizability of the predictive model presented here to broader MCI populations would require further external validation. In addition, the cohort was selected for only those with single- or multidomain aMCI and does not include those with MCI who do not have prominent episodic and logical memory impairment. Applying our probability model to other categories of patients is not advised. In addition, there was a higher adverse event rate in the donepezil group and a trend toward increased dropout in this group. This may have affected the heterogeneity of the cohort that remained in the trial. Furthermore, all clinical trials have a propensity toward selection biases in general level of health and education and tend not to represent most community populations. It should also be noted that our current analysis does not assess rates of progression from aMCI to AD, but rather risk of progression over 3 years. By doing this, the analysis is consistent with the primary endpoint of the clinical drug trial and alleviates the need to account for drug effects on progression. There were no drug effects for the primary endpoint of progression at 3 years. Nonetheless, we included drug arm in our current analysis to control for the effect of donepezil and vitamin E in our model. Furthermore, the probability calculations provide here are most accurate for the range of scores that were obtained in our cohort. Scores outside this range are extrapolated and may not be as accurate. Last, it must be noted that aMCI, as an independent disease concept, is somewhat controversial.[52,53] Regardless, the statistical model presented here offers a tool for predicting progression from this stage of early cognitive deficits to AD as defined by NINCDS-ADRDA criteria.

Our current model focused on neurocognitive measures. Notably, there were significant differences between progressors and nonprogressors on overall dementia severity and functional status as shown in table 2. The CDR, GDS, or ADL scale may be good predictors of progression from aMCI to AD, although this hypothesis was not tested in our current regression analyses. This was done to stay true to our hypothesis-driven analyses regarding assessment of neurocognitive measures in progression of aMCI to AD and to be parsimonious in our selection of model variables. In addition, the reduced model presented here, using only domain-specific instruments, resulted in a less accurate final predictive model than when the ADAS-cog and MMSE were included. However, given that the three neurocognitive tests in the reduced model are brief and common, it may be reasonable to accept a 4% loss of accuracy for improved clinical utility.

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REFERENCES

1. Albert MS, Moss MB, Tanzi R, Jones K. Preclinical prediction of AD using neuropsychological tests. J Int Neuropsychol Soc 2001;7:631–639.
2. Tierney MC, Szalai JP, Snow WG, et al. Prediction of probable Alzheimer's disease in memory-impaired patients: a prospective longitudinal study. Neurology 1996; 46:661–665.
3. Palmer K, Wang HX, Backman L, Winblad B, Fratiglioni L. Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project. Am J Psychiatry 2002;159:436–442.
4. Hanninen T, Hallikainen M, Koivisto K, et al. A follow-up study of age-associated memory impairment: neuropsychological predictors of dementia. J Am Geriatr Soc 1995;43:1007–1015.
5. Cooper B, Bickel H, Schaufele M. Early development and progression of dementing illness in the elderly: a general-practice based study. Psychol Med 1996;26:411–419.

6. Devanand DP, Folz M, Gorlyn M, Moeller JR, Stern Y. Questionable dementia: clinical course and predictors of outcome. J Am Geriatr Soc 1997;45:321–328.
7. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. Neurology 2002;59:198–205.
8. Tian J, Bucks RS, Haworth J, Wilcock G. Neuropsychological prediction of conversion to dementia from questionable dementia: statistically significant but not yet clinically useful. J Neurol Neurosurg Psychiatry 2003;74:433–438.
9. Artero S, Tierney MC, Touchon J, Ritchie K. Prediction of transition from cognitive impairment to senile dementia: a prospective, longitudinal study. Acta Psychiatr Scand 2003;107:390–393.
10. Griffith HR, Netson KL, Harrell LE, Zamrini EY, Brockington JC, Marson DC. Amnestic mild cognitive impairment: Diagnostic outcomes and clinical prediction over a two-year time period. J Int Neuropsychol Soc 2006;12:166–175.
11. Devanand DP, Pelton GH, Zamora D, et al. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. Arch Neurol 2005;62:975–980.
12. Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. JAMA 1995;273:1274–1278.
13. Visser PJ, Verhey FRJ, Ponds RWHM, Cruts M, van Broeckhoven CL, Jolles J. Course of objective memory impairment in non-demented subjects attending a memory clinic and predictors of outcome. Int J of Geriatr Psychiatry 2000;15:363–372.
14. Visser PJ, Verhey FR, Scheltens P, et al. Diagnostic accuracy of the Preclinical AD Scale (PAS) in cognitively mildly impaired subjects. J Neurol 2002;249:312–319.
15. Tierney MC, Szalai JP, Snow WG, et al. A prospective study of the clinical utility of ApoE genotype in the prediction of outcome in patients with memory impairment. Neurology 1996;46:149–154.
16. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Mild cognitive impairment in different functional domains and incident Alzheimer's disease. J Neurol Neurosurg Psychiatry 2005;76:1479–1484.
17. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379–2388.
18. Grundman M, Petersen RC, Ferris SH, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004;61:59–66.
19. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
20. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–1142.
21. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
22. Wechsler D. WMS-R Wechsler Memory Scale-Revised Manual. New York: The Psychological Corporation, Harcourt Brace Jovanovich, Inc., 1987.
23. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
24. Mohs RC. The Alzheimer's Disease Assessment Scale. Int Psychogeriatr 1996;8:195–203.
25. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.
26. Mohs R, Marin D, Green CR, Davis KL. The Alzheimer's disease assessment scale: modifications that can enhance its use in future clinical trials. In: Becker R, Giacobini E, eds. Alzheimer Disease: From Molecular Biology to Therapy. Boston: Birkhauser, 1996:407–411.
27. Kluger A, Ferris SH, Golomb J, Mittelman MS, Reisberg B. Neuropsychological prediction of decline to dementia in nondemented elderly. J Geriatr Psychiatry Neurol 1999;12:168–179.
28. Smith A. Symbol Digit Modalities Test Manual-Revised. Los Angeles: Western Psychological Services, 1982.
29. Monsch AU, Bondi MW, Butters N, Salmon DP, Katzman R, Thal LJ. Comparisons of verbal fluency tasks in the detection of dementia of the Alzheimer type. Arch Neurol 1992;49:1253–1258.
30. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale (ADAS) that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Dis 1997;11:13S–21S.
31. Kaplan EF, Goodglass H, Weintraub S. Boston Naming Test. Philadelphia: Lea & Febiger, 1983.
32. Wechsler D. Manual for the Wechsler Adult Intelligence Scale (rev. ed.). New York: The Psychological Corporation, Harcourt Brace Jovanovich, Inc., 1981.
33. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.
34. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11:33S–39S.
35. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136–1139.
36. Tibshirani R. Regression Shrinkage and Selection via the LASSO. J R Stat Soc Series B (Methodological) 1996;58:267–288.
37. Tierney MC, Yao C, Kiss A, McDowell I. Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. Neurology 2005;64:1853–1859.
38. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC. Mild cognitive impairment: prevalence and incidence according to different diagnostic criteria. Results of the Leipzig Longitudinal Study of the Aged (LEILA75+). Br J Psychiatry 2003;182:449–454.
39. Greene JD, Baddeley AD, Hodges JR. Analysis of the episodic memory deficit in early Alzheimer's disease: evidence from the doors and people test. Neuropsychologia 1996;34:537–551.

40. Rapp MA, Reischies FM. Attention and executive control predict Alzheimer disease in late life: results from the Berlin Aging Study (BASE). Am J Geriatr Psychiatry 2005;13:134–141.
41. Baudic S, Barba GD, Thibaudet MC, Smagghe A, Remy P, Traykov L. Executive function deficits in early Alzheimer's disease and their relations with episodic memory. Arch Clin Neuropsychol 2006;21:15–21.
42. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. Neurology 1998;51:728–733.
43. Amieva H, Letenneur L, Dartigues JF, et al. Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. Dement Geriatr Cogn Disord 2004;18:87–93.
44. Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004;63:1882–1891.
45. Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. Neurology 2006;66:828–832.
46. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. JAMA 1994;271:1004–1010.
47. White L, Katzman R, Losonczy K, et al. Association of education with incidence of cognitive impairment in three established populations for epidemiologic studies of the elderly. J Clin Epidemiol 1994;47:363–374.
48. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Arch Gen Psychiatry 1998;55:809–815.
49. Aggarwal N, Wilson R, Beck T, et al. The apolipoprotein E epsilon4 allele and incident Alzheimer's disease in persons with mild cognitive impairment. Neurocase 2005;11:3–7.
50. Bennett DA, Wilson RS, Schneider JA, et al. Apolipoprotein E epsilon4 allele, AD pathology, and the clinical expression of Alzheimer's disease. Neurology 2003;60:246–252.
51. Fleisher A, Grundman M, Jack CR Jr, et al. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol 2005;62:953–957.
52. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology 2006;67:467–473.
53. Morris JC, Cummings J. Mild cognitive impairment (MCI) represents early-stage Alzheimer's disease. J Alzheimers Dis 2005;7:235–239; discussion 255–262.