# Comparing predictors of conversion and decline in mild cognitive impairment

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## ABSTRACT

**Objective:** A variety of measurements have been individually linked to decline in mild cognitive impairment (MCI), but the identification of optimal markers for predicting disease progression remains unresolved. The goal of this study was to evaluate the prognostic ability of genetic, CSF, neuroimaging, and cognitive measurements obtained in the same participants.

**Methods:** *APOE* $\epsilon$4 allele frequency, CSF proteins ($A\beta_{1\text{-}42}$, total tau, hyperphosphorylated tau [$p\text{-tau}_{181p}$]), glucose metabolism (FDG-PET), hippocampal volume, and episodic memory performance were evaluated at baseline in patients with amnestic MCI (n = 85), using data from a large multisite study (Alzheimer's Disease Neuroimaging Initiative). Patients were classified as normal or abnormal on each predictor variable based on externally derived cutoffs, and then variables were evaluated as predictors of subsequent conversion to Alzheimer disease (AD) and cognitive decline (Alzheimer's Disease Assessment Scale–Cognitive Subscale) during a variable follow-up period (1.9 ± 0.4 years).

**Results:** Patients with MCI converted to AD at an annual rate of 17.2%. Subjects with MCI who had abnormal results on both FDG-PET and episodic memory were 11.7 times more likely to convert to AD than subjects who had normal results on both measures ($p \leq 0.02$). In addition, the CSF ratio $p\text{-tau}_{181p}/A\beta_{1\text{-}42}$ ($\beta$ = 1.10 ± 0.53; $p$ = 0.04) and, marginally, FDG-PET predicted cognitive decline.

**Conclusions:** Baseline FDG-PET and episodic memory predict conversion to AD, whereas $p\text{-tau}_{181p}/A\beta_{1\text{-}42}$ and, marginally, FDG-PET predict longitudinal cognitive decline. Complementary information provided by these biomarkers may aid in future selection of patients for clinical trials or identification of patients likely to benefit from a therapeutic intervention. ***Neurology*®** **2010;75:230–238**

## GLOSSARY

**AD** = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–Cognitive Subscale; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **AVLT** = Auditory Verbal Learning Test; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **FDG** = [$^{18}$F]fluorodeoxyglucose; **MCI** = mild cognitive impairment; **MNI** = Montreal Neurological Institute; **$p\text{-tau}_{181p}$** = hyperphosphorylated tau; **ROC** = receiver operating characteristic; **t-tau** = total tau.

Individuals with mild cognitive impairment (MCI) are a target population for evaluating very early treatment interventions for Alzheimer disease (AD) since they represent an intermediate stage between normal function and AD, and are at higher risk for decline than healthy older individuals. Because individuals with MCI decline at different rates and some never develop AD, there is a need for tools to select patients with MCI who would benefit most from treatment. Existing research has implicated a number of biomarkers that predict cognitive

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Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators is available in appendix e-2 at www.neurology.org.

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decline or conversion to AD in this population, including glucose metabolism reductions, measured by [$^{18}$F]fluorodeoxyglucose uptake (FDG-PET) in parietal, posterior cingulate, and temporal brain regions[1,2]; MRI evidence of medial temporal lobe and hippocampal atrophy[3-6]; increased CSF total tau (t-tau) and hyperphosphorylated tau (p-tau$_{181p}$), indicating neurofibrillary tangle pathology, and decreased A$\beta_{1-42}$, indicating amyloid (A$\beta$) plaque pathology[7-9]; and presence of the apolipoprotein E (*APOE*) $\varepsilon$4 allele.[10] While each of these measures has independently shown promise for predicting disease progression,[11] they have not yet been compared to one another in the same patient population. Furthermore, the relative value of biomarkers compared to neuropsychological tests is not well-understood. Word list learning ability, a form of episodic memory, is a particularly well-studied and strong predictor of conversion.[12-14] A number of studies have compared the predictive value of 2 or more biomarkers at a time, such as MRI and CSF,[15,16] MRI and cognitive testing,[17-19] FDG-PET and CSF,[8] FDG-PET and cognitive testing,[20] and MRI, CSF, and FDG-PET,[21] but findings have been inconsistent, likely due to small sample sizes and a variety of methodologic factors.

In this study, we used MCI participant data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multicenter project with approximately 50 medical center and university sites across the United States and Canada. ADNI is supported by the NIH, private pharmaceutical companies, and nonprofit organizations, and has the primary goal of evaluating MRI, PET, CSF, and clinical measures acquired serially over 2–3 years.

We compared the prognostic ability of a number of candidate biomarkers that were obtained at baseline to determine which marker or combination of markers is optimal for predicting both conversion to AD and cognitive decline. Determination of sensitive and specific markers of very early AD progression is intended to help develop new treatments and to decrease the time and cost of clinical trials.

## METHODS

**Subjects.** A total of approximately 200 cognitively normal older subjects, 400 subjects with MCI, and 200 patients with early AD are enrolled in ADNI, all of whom have had MRI scanning, approximately 50% have had PET scanning, and approximately 50% also agreed to lumbar puncture. As of April 2009, a subset of 85 subjects with MCI had baseline data available for all measures of interest and were used for this study. Serial clinical diagnostic assessments were carried out at 6, 12, 18, 24, and 36 months. Approximately 8% of subjects completed 3 visits (12 mo), 15% completed 4 visits, the majority, 72%, completed 5 visits (24 mo), and the remaining 5% completed 6 visits (36 mo). Conversion to AD was established at individual recruitment sites, with review centrally, and none of the variables used in the prediction of outcome were used as indicators of conversion. An examination of each measure for outliers revealed that 3 subjects had abnormally high t-tau, p-tau$_{181p}$, or both ($Z$ score >3), so they were excluded from tests that involved these measurements.

Full inclusion/exclusion criteria are described in detail at www.adni-info.org. Briefly, all subjects were between ages 55 and 90 years, had completed at least 6 years of education, were fluent in Spanish or English, and were free of any other significant neurologic diseases. Subjects with MCI were classified as single-domain or multidomain amnestic MCI,[22] normal subjects had Clinical Dementia Rating (CDR) scores of 0, and patients with AD met standard diagnostic criteria.[23]

The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)[24] and diagnostic status (remaining stable as MCI or converting to AD) were the outcome variables of interest. The ADAS-Cog contains 11 items assessing fundamental cognitive functions (language, memory, praxis, comprehension), and the total score ranges from 0 to 70, with a higher score indicating poorer cognitive function.

Candidate predictors included presence of an *APOE* $\epsilon$4 allele, neuroimaging measurements (FDG-PET, hippocampal volume), CSF biomarkers (A$\beta_{1-42}$, t-tau, p-tau$_{181p}$), and episodic memory performance on the Auditory Verbal Learning Test (AVLT), all obtained at baseline.

**Standard protocol approvals, registrations, and patient consents.** The procedures for this study were approved by institutional review boards of all participating institutions. All subjects gave written, informed consent to blood sampling, lumbar puncture, cognitive testing, and neuroimaging prior to participation.

**Biomarker predictors.** ***Episodic memory.*** The total number of words correctly recalled on all 5 immediate recall trials of the AVLT[25] was assessed at baseline and used as a predictor variable in our analysis because recent studies have shown that word list learning in particular is a predictor of conversion compared to other neuropsychological tests.[12-14]

***Genetic.*** *APOE* genotypes were determined for all ADNI subjects through analysis of blood samples that was carried out at the University of Pennsylvania Alzheimer's Disease Biomarker Laboratory.

***Hippocampal volume.*** Structural magnetic resonance scans (1.5-T) were acquired at multiple ADNI sites using a standardized MRI protocol described elsewhere.[26] Bilateral hippocampal volumes were obtained using Freesurfer software (http://surfer.nmr.mgh.harvard.edu), an atlas-based approach that has been validated for use in subjects with a great deal of morphologic variability.[27] More information is provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

***CSF biomarkers.*** CSF biomarker variables included A$\beta_{1-42}$, t-tau, and p-tau, phosphorylated at threonine 181, in pg/mL (p-tau$_{181p}$), as well as ratios (t-tau/A$\beta_{1-42}$, p-tau$_{181p}$/A$\beta_{1-42}$).

Methods for analysis have been previously described[28] and are provided online.

***FDG-PET.*** ADNI PET data were acquired at sites nationwide using a protocol described elsewhere (http://www.loni.ucla.edu/ADNI/Data/ADNI_Data.shtml). Briefly, PET images were acquired 30–60 minutes postinjection. Images were averaged, spatially aligned, interpolated to a standard voxel size, intensity normalized, and smoothed to a common resolution of 8-mm full width at half maximum. Spatial normalization of each individual's PET volume to the standard $^{15}O$-$H_2O$ PET template was conducted using SPM5[29] (template voxel dimensions: 91 × 109 × 91; voxel size: 2 mm × 2 mm × 2 mm). PET volumes were intensity normalized to a single region made up of the cerebellar vermis, defined by the AAL region within the Montreal Neurological Institute (MNI) atlas, and the pons, defined by manual tracing on the MNI template. Methods for analysis have been previously described[30] and are provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

**Table 1** Means (SD) of demographic and cognitive measures are shown for all subject groups, and baseline variables of interest are shown for nonconverter and converter subjects with MCI[a]

| | | | MCI | | |
|---|---|---|---|---|---|
| | AD | Normal | Converters | Nonconverters | *p* |
| No. | 193 | 229 | 28 | 57 | |
| M/F | 102/91 | 119/109 | 19/9 | 37/20 | NS |
| Age, y | 78.2 (7.5) | 79.0 (5.0) | 78.3 (7.5) | 78.0 (7.4) | NS |
| Education, y | 14.7 (3.1) | 16.0 (2.9) | 16.4 (2.6) | 16.3 (2.8) | NS |
| ADAS-Cog (baseline) | 18.6 (6.3) | 6.2 (2.9) | 13.2 (4.6) | 10.3 (3.9) | 0.003* |
| MMSE (baseline) | 23.4 (2.0) | 29.1 (1.0) | 26.4 (1.7) | 27.3 (1.6) | 0.03* |
| Predictor variables of interest | | | | | |
| Total follow-up time, y | | | 1.9 (0.4) | 1.9 (0.4) | NS |
| Genetic | | | | | |
| *APOE* ϵ4 percentage | | | 0.41 | 0.25 | 0.07 |
| Neuroimaging | | | | | |
| FDG-PET | | | 1.13 (0.10) | 1.22 (0.14) | 0.04* |
| Hippocampal volume, $mm^3$ | | | 2,883 (558) | 3,187 (527) | 0.06 |
| CSF biomarkers, pg/mL | | | | | |
| $A\beta_{1-42}$ | | | 149.7 (45.3) | 165.7 (57.9) | 0.16 |
| p-$tau_{181p}$ | | | 37.1 (10.7) | 34.3 (17.8) | 0.02* |
| t-tau | | | 94.0 (28.1) | 100.6 (55.3) | 0.11 |
| p-$tau_{181p}$/$A\beta_{1-42}$ | | | 0.27 (0.12) | 0.25 (0.18) | 0.01* |
| t-tau/$A\beta_{1-42}$ | | | 0.68 (0.27) | 0.75 (0.62) | 0.13 |
| Memory | | | | | |
| AVLT | | | 26.4 (6.6) | 32.2 (8.1) | 0.01* |

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; AVLT = Auditory Verbal Learning Test; FDG = [$^{18}$F]fluorodeoxyglucose; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; p-$tau_{181p}$ = hyperphosphorylated tau; t-tau = total tau.

[a] Values are mean (SD). Significant *p* values (*$p < 0.05$) and trends ($0.05 < p < 0.10$) are shown for tests of differences between converter and nonconverter groups using continuous forms of the variables. Note that for ADAS-Cog, t-tau, p-$tau_{181p}$, t-tau/$A\beta_{1-42}$, and p-$tau_{181p}$/$A\beta_{1-42}$, a higher mean is associated with greater impairment, whereas for the other measures a lower mean is associated with greater impairment.

**Cutoffs for subject classification.** Dichotomous forms of all independent variables (defined as AD+/AD−) with the exception of *APOE* were established using receiver operating characteristic (ROC) analyses with AD and cognitively normal ADNI participants to determine optimal cutoffs for each measure. Cutoffs for each variable were selected by choosing the threshold that optimized both sensitivity and specificity, and were subsequently used to categorize subjects with MCI as AD+ or AD− on each measure. ROC analyses were carried out using all available ADNI data for each measure.

For *APOE*, subjects were divided based on the presence (AD+) or absence (AD−) of at least one *APOE* ϵ4 allele.

**Statistical analyses.** Statistical analyses were carried out using SPSS 16.0. Independent samples *t*, Mann-Whitney *U*, and $\chi^2$ tests were used to assess differences between converter and nonconverter groups on each measure and associations between dichotomized variables. Positive predictive value was calculated as the number of MCI converters correctly classified as AD+ divided by all MCI converters, and negative predictive value was the number of MCI nonconverters correctly classified as AD− divided by all MCI nonconverters.

Both univariate and multivariate models were examined to assess the degree to which each baseline predictor was associated with the outcome measure independently or in conjunction with the other variables. However, due to overlap in AD+/AD− status among CSF measures (table e-2 in appendix e-1), only one CSF measure could be included in multivariate models. p-$tau_{181p}$/$A\beta_{1-42}$ was selected because it showed the strongest prediction of conversion at the univariate level. Thus, 5 variables were included in the multivariate analyses: *APOE* status, FDG-PET, hippocampal volume, p-$tau_{181p}$/$A\beta_{1-42}$, and AVLT recall.

For the Cox proportional hazards models predicting conversion, the time variable was amount of time (in years) from baseline to the visit in which AD was diagnosed, or to the most recent visit for censored cases. In the mixed effects models, the outcome measure consisted of all available serial ADAS-Cog measurements, which incorporated individual variability in the number of completed visits, missing data, and individual variability in between-scan intervals.[31] Each model included a random intercept to account for variability in individual starting point, and time between visits (in years since the initial visit) was computed separately for each individual. The interaction term for each independent variable of interest × time represents the degree to which that variable was associated with change in the ADAS-Cog over time.

Assumptions of linearity were verified for each model. Age, education, and sex were included as covariates in all models, and all statistical tests were evaluated for statistical significance at $\alpha = 0.05$, 2-sided, and trends at $0.05 < \alpha < 0.10$.

## RESULTS

**Differences between converters and nonconverters.** Table 1 summarizes demographic information for all groups (AD, MCI, normal), baseline measurements for converter and nonconverter MCI groups, and statistical differences between converter and nonconverter groups. Of the 85 MCI participants, 28 (32.9% total, or an annual rate of 17.2%) converted to AD. None of the subjects with MCI reverted to a normal diagnosis or converted to a non-Alzheimer dementia. Converters and nonconverters did not differ on demographic characteristics, but were either significantly or marginally different on

**Table 2** Normal, MCI, and AD subjects with available data for all measures of interest and ROC analysis results

| | | Neuroimaging | | CSF biomarkers | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Genetic: *APOE* $\epsilon4$ | FDG-PET | Hippocampal volume | $A\beta_{1-42}$ | p-tau$_{181p}$ | t-tau | p-tau$_{181p}$/$A\beta_{1-42}$ | t-tau/$A\beta_{1-42}$ | Memory: AVLT |
| **Sample sizes**[a] | | | | | | | | | |
| AD | 193 | 97 | 146 | 102 | 102 | 100 | 102 | 100 | 193 |
| MCI | 85 | 85 | 85 | 85 | 84 | 83 | 83 | 83 | 85 |
| Normal | 227 | 102 | 198 | 114 | 114 | 114 | 114 | 114 | 229 |
| **ROC curve analyses (AD and normal)**[b] | | | | | | | | | |
| ROC AUC | | 0.88 | 0.89 | 0.81 | 0.80 | 0.80 | 0.84 | 0.85 | 0.95 |
| Threshold value | | 1.21 | 3,260.40 | 165.50 | 26.10 | 86.80 | 0.14 | 0.46 | 33.50 |
| Sensitivity, % | | 82 | 79 | 82 | 80 | 71 | 87 | 85 | 93 |
| Specificity, % | | 70 | 82 | 70 | 70 | 77 | 70 | 78 | 88 |
| Overall accuracy, % | | 76 | 81 | 76 | 75 | 74 | 78 | 81 | 90 |
| **Positive/negative predictive value (MCI), %** | | | | | | | | | |
| Positive predictive value | 40 | 41 | 41 | 38 | 42 | 42 | 42 | 39 | 41 |
| Negative predictive value | 74 | 79 | 78 | 76 | 83 | 73 | 87 | 76 | 88 |

Abbreviations: AD = Alzheimer disease; AUC = area under the curve; AVLT = Auditory Verbal Learning Test; FDG = [$^{18}$F]fluorodeoxyglucose; MCI = mild cognitive impairment; p-tau$_{181p}$ = hyperphosphorylated tau; ROC = receiver operating characteristic; t-tau = total tau.

[a] The number of subjects with AD and normal subjects with available data varied for each measure.

[b] ROC analyses using available data for subjects with AD and normal subjects were carried out to establish threshold values for abnormal (AD+) and normal (AD−) cutoffs used in subsequent models. The AUC, threshold values used as cutoffs, and the sensitivity, specificity, and overall accuracy (calculated using subjects with AD and normal subjects) are shown for each measure. The positive predictive value (percent MCI converters correctly classified as AD+) and negative predictive value (percent MCI nonconverters correctly classified as AD−) were also calculated for subjects with MCI using the ROC-derived cutoffs.

cognitive variables and predictor variables of interest. Agreement between AD+ and AD− categorizations across variables is reported online.

**Classification of AD+ and AD− subjects.** Table 2 summarizes the numbers of normal subjects, subjects with MCI, and subjects with AD with available data for all measures of interest, and the ROC analysis results, which include the area under the curve (range 0.80–0.95), threshold value, sensitivity (range 71%–93%), specificity (range 70%–88%), and overall accuracy (range 74%–90%) for classification of normal subjects and subjects with AD with each measure. Finally, the thresholds for each measure were applied to the MCI participants to determine positive and negative predictive values for conversion.

**Cox proportional hazards models: Predicting conversion.** In univariate models, several variables were associated with increased risk of conversion to AD. As shown in table 3, subjects categorized as AD+ on FDG-PET, hippocampal volume, p-tau$_{181p}$, p-tau$_{181p}$/$A\beta_{1-42}$, AVLT, and, marginally, *APOE* had a higher risk of converting than AD− subjects on each measure (hazard ratio range 2.94–4.68). In the multivariate model, only FDG-PET and AVLT remained significant predictors. Specifically, subjects who were AD+ on FDG-PET had a 2.72 ($p = 0.05$) greater risk of converting to AD than subjects who were AD− on FDG-PET (figure, A), assuming equal AD+ status on the other variables, and this risk was 4.30 ($p = 0.02$) for AVLT (figure, B). Taken together, these findings indicate that the 36 subjects (42%) who were AD+ for both FDG-PET and AVLT had an 11.7-fold (95% confidence interval [CI] 2.22–61.75) greater risk of converting to AD than subjects categorized as AD− on both measures.

**Mixed effects models: Predicting cognitive decline.** Average decline on the ADAS-Cog was 1.11 ADAS-Cog points/year (95% CI 0.69–1.53). All baseline variables predicted subsequent ADAS-Cog decline in univariate models, although AVLT was marginally significant (table 3). In the multivariate model, high p-tau$_{181p}$/$A\beta_{1-42}$ remained a significant predictor ($p = 0.04$), low FDG-PET was a marginally significant ($p = 0.09$) predictor, and no other variables were significant ($p > 0.33$). The 43 subjects (51%) who were AD+ on p-tau$_{181p}$/$A\beta_{1-42}$ had an increased ADAS-Cog annual decline rate of 1.10 units/year compared with AD− subjects, accounting for all other variables (0.77 units/year for FDG-PET).

**DISCUSSION** The goal of this multicenter longitudinal study was to compare a variety of candidate predictors of decline in MCI over a follow-up period of approximately 2 years. All of these biomarkers

**Table 3** Results of Cox proportional hazards models, with potential conversion to AD as the outcome measure, and mixed effects models, with ADAS-Cog change as the outcome measure[a]

| | Conversion to AD | | Cognitive decline | |
|---|---|---|---|---|
| | Univariate | Multivariate | Univariate | Multivariate |
| *APOE* $\epsilon$4 | | | | |
| $\beta \pm$ SE | 0.66 ± 0.40 | NS | 0.87 ± 0.43 | NS |
| HR (95% CI) | 1.94 (0.89–4.21) | | | |
| *p* | 0.10 | | 0.04* | |
| FDG-PET | | | | |
| $\beta \pm$ SE | 1.08 ± 0.045 | 1.00 ± 0.51 | 1.26 ± 0.43 | 0.77 ± 0.46 |
| HR (95% CI) | 2.94 (1.23–7.04) | 2.72 (0.99–7.47) | | |
| *p* | 0.02* | 0.05* | 0.003* | 0.09 |
| Hippocampal volume | | | | |
| $\beta \pm$ SE | 0.91 ± 0.45 | NS | 0.94 ± 0.43 | NS |
| HR (95% CI) | 2.49 (1.02–5.96) | | | |
| *p* | 0.04* | | 0.03* | |
| CSF biomarkers | | | | |
| $A\beta_{1-42}$ | | | | |
| $\beta \pm$ SE | NS | | 1.14 ± 0.46 | |
| HR (95% CI) | | | | |
| *p* | | | 0.01* | |
| p-tau$_{181p}$ | | | | |
| $\beta \pm$ SE | 1.06 ± 0.50 | | 1.54 ± 0.44 | |
| HR (95% CI) | 2.88 (1.09–7.59) | | | |
| *p* | 0.03* | | <0.001* | |
| t-tau | | | | |
| $\beta \pm$ SE | NS | | 1.12 ± 0.43 | |
| HR (95% CI) | | | | |
| *p* | | | 0.01* | |
| p-tau$_{181p}$/A$\beta_{1-42}$ | | | | |
| $\beta \pm$ SE | 1.38 ± 0.62 | NS | 1.74 ± 0.47 | 1.10 ± 0.53 |
| HR (95% CI) | 3.99 (1.19–13.32) | | | |
| *p* | 0.03* | | <0.001* | 0.04* |
| t-tau/A$\beta_{1-42}$ | | | | |
| $\beta \pm$ SE | NS | | 1.22 ± 0.45 | |
| HR (95% CI) | | | | |
| *p* | | | 0.008* | |
| AVLT | | | | |
| $\beta \pm$ SE | 1.54 ± 0.63 | 1.46 ± 0.64 | 0.83 ± 0.47 | NS |
| HR (95% CI) | 4.68 (1.37–15.98) | 4.30 (1.24–14.97) | | |
| *p* | 0.01* | 0.02* | 0.08 | |

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; AVLT = Auditory Verbal Learning Test; CI = confidence interval; FDG = [$^{18}$F]fluorodeoxyglucose; HR = hazard ratio; p-tau$_{181p}$ = hyperphosphorylated tau; t-tau = total tau.

[a] Parameter estimates ($\beta$) and standard error (SE) are shown for all models, and HRs are shown. Univariate models evaluated each predictor variable individually (left column), and multivariate models (right column) evaluated *APOE* $\epsilon$4 allele frequency, FDG-PET, hippocampal volume, p-tau$_{181p}$/A$\beta_{1-42}$, and AVLT in the same model. Blank boxes appear for predictors that were not included in multivariate models. Significant *p* values (*$p < 0.05$) and trends ($0.05 < p < 0.10$) are shown. See Methods for details.

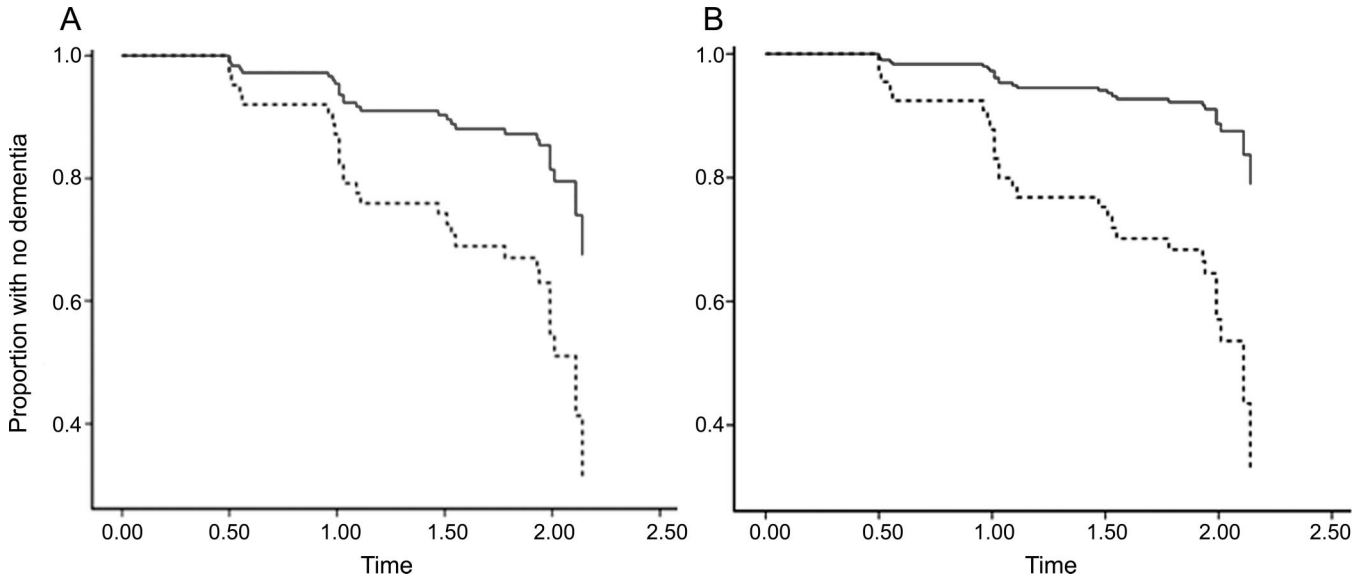
were significant predictors of conversion or decline in univariate models. In multivariate models predicting conversion, glucose metabolism and episodic memory function were significant. Individuals who were abnormal (AD+) on both FDG-PET and AVLT were 11.7 times more likely to convert to AD than individuals who were normal on these measures. In multivariate models predicting decline, the CSF ratio p-tau$_{181p}$/A$\beta_{1-42}$ (and, marginally, FDG-PET) were significant when accounting for all the other variables.

There were several noteworthy features of our approach. First, cutoffs used to classify subjects with MCI as abnormal or normal on each predictor variable were derived from an independent sample, and are therefore potentially applicable outside of this population. Second, all predictors were defined a priori, as opposed to frequently used exploratory methods, such as voxel-wise analyses for PET and MRI data, that are optimized for a study-specific dataset. The availability of data through ADNI made it possible to directly compare all of these predictors in the same individuals for the first time. Finally, the use of dichotomous predictors, as opposed to a continuous variable, provides a precise way of selecting individual subjects with MCI for a clinical trial or potential treatment.

The fact that different combinations of markers predict conversion status and cognitive decline suggests that these markers may track different aspects of disease progression. Predictors associated with conversion (AVLT and FDG-PET) likely reflect disease severity, i.e., how close an individual is to a significant clinical transition. On the other hand, predictors associated with cognitive decline (primarily CSF p-tau$_{181p}$/A$\beta_{1-42}$, and secondarily FDG-PET) likely reflect rate of change, independent of absolute disease severity.

Studies comparing the predictive value of multiple biomarkers have been variable, although several useful meta-analyses or reviews have summarized recent findings.[11,32-34] Our data are consistent with reports of the predictive value of CSF biomarkers,[35,36] and a recent large, multicenter study that is one of the few to use externally derived cutoffs.[7] Our results are consistent with previous reports of the predictive value of FDG-PET,[1] studies that have examined both FDG-PET and *APOE*,[37,38] and a report that FDG-PET was superior to the Mattis dementia scale.[20] Our findings are not in agreement, however, with recent data indicating that MRI and PET were superior to CSF in predicting cognitive decline.[21] Additionally, although we found that FDG-PET and AVLT performance were the best predictors of conversion, our univariate findings are consistent with

**Figure** FDG-PET and AVLT survival curves show increased conversion over time for abnormal relative to normal subjects




Predicted survival curves based on Cox proportional hazards models (table 3) illustrate the univariate results for (A) FDG-PET and (B) AVLT, which were the 2 variables that remained significant in the multivariate model. Both curves show that for each variable, a higher proportion of AD− subjects (solid black line) remained dementia-free over time compared to AD+ subjects (dotted line). Age, education, and sex were included as control covariates. Proportion of subjects remaining dementia-free is shown on the y-axis.

studies showing that MRI and CSF,[15,16,39] MRI and cognition,[17] and MRI and *APOE*ε4[40] measures are useful for predicting conversion to AD, although others have suggested that MRI measures are superior to cognitive measures in predicting decline.[18,19] Finally, although studies of AD conversion frequently do not account for rates of conversion or time-dependent change as we have done here, our results are also consistent with one study that did account for time and compared p-tau$_{181p}$, t-tau, and FDG-PET and found that p-tau$_{181p}$ optimally predicted cognitive decline, while FDG-PET optimally predicted conversion.[8]

Inconsistencies in recent findings are likely due to a variety of methodologic issues such as differences in neuroimaging processing techniques and variable selection, CSF protein immunoassay techniques, criteria for setting cutoff points for subject categorization, study design, and statistical analysis. Importantly, few studies on AD prediction define predictor variables before evaluating their performance; instead, a "predictive" measure is developed based on differences between MCI converters and nonconverters and retrospectively applied to the initial population without validating it in an independent population (often due to sample size constraints).

An important limitation of our findings is that the hippocampal and FDG-PET ROIs may not be optimized for this sample. Whole-brain, data-driven, voxel-based, or other approaches to the analysis of PET or magnetic resonance data might have resulted in stronger prediction outcomes for the imaging variables. Hippocampal volume was a significant predictor of decline at the univariate but not multivariate level, suggesting that the association between hippocampal volume and decline may be mediated in part by the other measures in our analysis. In contrast, other studies have reported a stronger role for hippocampal or other structural measurements in predicting decline,[3] even when examined in conjunction with CSF measurements.[16,41] However, the regions of interest that we selected were study independent, frequently associated with decline in AD and MCI, and obtained through an automated and standardized processing stream and are therefore strong candidate measurements for clinical trials of therapeutic treatments.

There are several other limitations of this study that deserve comment. First, these models are based on the subset of MCI participants who agreed to participate in all biomarker testing, and future studies will be needed to address the question of whether our findings generalize to a broader sample, and whether differences exist for single-domain and multidomain MCI or for patients with amnestic MCI who convert to non-Alzheimer dementias. Second, our results may depend on the number and precise combination of predictor variables included in the model. A longer follow-up period may also result in model changes, since the value of predictors is likely modulated by the phase of disease. Clinical diagnosis of AD involves factors that are difficult to standardize

and involves some degree of subjectivity and uncertainty. Furthermore, there are other cognitive measures and biomarkers that may play important roles in prediction that were not addressed here (such as the CDR–sum of boxes, Mini-Mental State Examination, genetic markers, and diffusion tensor imaging measures). Importantly, forthcoming ADNI data using PET tracers for A$\beta$ deposition will help elucidate the role of brain amyloid load in patient outcomes.

The current clinical role of these, and other, biomarkers in dementia care is relatively limited largely because of the lack of effective treatment. However, our results suggest that these biomarkers could be effective in identifying patients with MCI who are more likely to progress to AD over relatively brief time periods. This approach could be useful for identifying patients who would benefit from treatment when it becomes available and for selecting subjects in clinical trials of therapeutic agents for MCI.

## AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Landau and Dr. Harvey.

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## DISCLOSURE

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Dr. Reiman serves on scientific advisory boards for Accera, Inc., AstraZeneca, Elan Corporation, Eli Lilly and Company, and GlaxoSmithKline; serves as a consultant to Amnestix/Sygnis; serves as Deputy Editor of the *Journal of Clinical Psychiatry*; holds a patent re: Methods for Tracking the Progression of Alzheimer's Disease Identifying Treatment Using Transgenic Mice and has patents pending re: Evaluation Of Treatment To Decrease The Risk Of Progressive Brain Disorder Or Slow Brain Aging, Methodologies Linking Patterns From Multi-Modality Datasets, and Methods of Diagnosing Alzheimer's Disease and Associated Genetic Markers; and receives research support from Kronos Life Sciences, GlaxoSmithKline, AstraZeneca, Avid Radiopharmaceuticals, Inc., the NIH (NIA 9 R01 AG031581-10 [PI]), and from the State of Arizona. 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Dr. Shaw has received funding for travel and speaker honoraria from Pfizer Inc; serves on the editorial board of *Therapeutic Drug Monitoring;* may potentially receive revenue for patent pending (application number 10/192,193): O-methylated rapamycin derivatives for alleviation and inhibition of lymphoproliferative disorders, licensed by the University of Pennsylvania to Novartis; receives royalties from publication of *Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring* (Wolters Kluwer/Lippincott Williams & Wilkins, 2005); receives research support from the NIH (AG024904 [Co-PI Biomarker Core Laboratory]); and receives board of directors' compensation and holds stock options in Saladax Biomedical. Dr. Trojanowski has received funding for travel and honoraria from Takeda Pharmaceutical Company Ltd. and to attend numerous conferences not funded by industry; serves as an Associate Editor of *Alzheimer's & Dementia*; may accrue revenue on patents re: Modified Avidin-Biotin Technique, Method of Stabilizing Microtubules to Treat Alzheimer's Disease, Method of Detecting Abnormally Phosphorylated Tau, Method of Screening for Alzheimer's Disease or Disease Associated with the Accumulation of Paired Helical Filaments, Compositions and Methods for Producing and Using Homogeneous Neuronal Cell Transplants, Rat Comprising Straight Filaments in Its Brain, Compositions and Methods for Producing and Using Homogeneous Neuronal Cell Transplants to Treat Neurodegenerative Disorders and Brain and Spinal Cord Injuries, Diagnostic Methods for Alzheimer's Disease by Detection of Multiple MRNAs, Methods and Compositions for Determining Lipid Peroxidation Levels in Oxidant Stress Syndromes and Diseases, Compositions and Methods for Producing and Using Homogenous Neuronal Cell Transplants, Method of Identifying, Diagnosing and Treating Alpha-synuclein Positive Neurodegenerative Disorders, Mutation-specific Functional Impairments in Distinct Tau Isoforms of Hereditary Frontotemporal Dementia and Parkinsonism Linked to Chromosome-17: Genotype Predicts Phenotype, Microtubule Stabilizing Therapies for Neurodegenerative Disorders; and Treatment of Alzheimer's and Related Diseases with an Antibody; and receives research support from the NIH (NIA P01 AG 09215-20 [PI], NIA P30 AG 10124-18 [PI], NIA PO1 AG 17586-10 [Project 4 Leader], NIA 1PO1 AG-19724-07 [Core C Leader], NIA 1 U01 AG 024904-05 [Co-PI Biomarker Core Laboratory], NINDS P50 NS053488-02 [PI], NIA UO1 AG029213-01 (Co-I); RC2NS069368 (PI), RC1AG035427 (PI), and NIA P30AG036468 [PI]), and from the Marian S. 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