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Prediction of conversion to Alzheimer's disease with longitudinal measures and time-to-event data

Kan Li[a], **Wenyaw Chan**[a], **Rachelle S. Doody**[b], **Joseph Quinn**[c], **Sheng Luo**[a,*], and **the Alzheimer's Disease Neuroimaging Initiative**

[a]Department of Biostatistics, The University of Texas Health Science Center at Houston, Houston, TX, USA [b]F. Hoffman-La Roche, Basel, Switzerland [c]Department of Neurology, Oregon Health and Science University and Portland VA Medical Center, Portland, OR, USA

Abstract

Background—Identifying predictors of conversion to Alzheimer's disease (AD) is critically important for AD prevention and targeted treatment.

Objective—To compare various clinical and biomarker trajectories for tracking progression and predicting conversion from amnestic mild cognitive impairment to probable AD.

Methods—Participants were from the ADNI-1 study. We assessed the ability of 33 longitudinal biomarkers to predict time to AD conversion, accounting for demographic and genetic factors. We used joint modelling of longitudinal and survival data to examine the association between changes of measures and disease progression. We also employed time-dependent receiver operating characteristic (ROC) method to assess the discriminating capability of the measures.

Results—23 of 33 longitudinal clinical and imaging measures are significant predictors of AD conversion beyond demographic and genetic factors. The strong phenotypic and biological predictors are in the cognitive domain (ADAS-Cog; RAVLT), functional domain (FAQ) and neuroimaging domain (middle temporal gyrus and hippocampal volume). The strongest predictor is ADAS-Cog 13 with an increase of one SD in ADAS-Cog 13 increased the risk of AD conversion by 2.92 times.

Conclusion—Prediction of AD conversion can be improved by incorporating longitudinal change information, in addition to baseline characteristics. Cognitive measures are consistently significant and generally stronger predictors than imaging measures.

Keywords

mild cognitive impairment; joint modeling; longitudinal and survival data; prediction; ADNI

[*]Corresponding author: Sheng Luo, PhD, Department of Biostatistics, School of Public Health, The University of Texas Health Science Center at Houston, 1200 Herman Pressler Dr, Rm E815, Houston, TX 77030, USA. Tel: +1-713-500-9554; sheng.t.luo@uth.tmc.edu.

Conflict of Interest

The authors have no conflict of interest to report.

1. Introduction

Mild cognitive impairment (MCI) often represents an intermediate stage between normal cognition and Alzheimer's disease (AD) [1], and individuals with MCI have been an increasingly common target population for evaluating prognosis and early treatment for AD. However, only a portion of MCI patients progress to dementia while some individuals remain stable or even revert to the normal cognitive status [2]. Identifying predictors of conversion to AD is therefore critically important for AD prevention and targeted treatment.

Existing research has implicated a number of biomarkers that predict conversion from MCI to AD or cognitive decline, including neuroimaging biomarkers [3–6], neuropsychological assessments [7–9], and biomedical biomarkers [10,11]. Most existing studies [12,13] of predicting time-to-AD adopt Cox regression models with baseline measures. Such an approach implicitly assumes that the predictors stay constant over the length of study, which is unlikely to be true in studies over an extensive period of time. Moreover, the majority of such studies [14,15], exploiting longitudinal measures for predicting future biomarkers or clinical score of MCI patients, fail to take into account dependent terminal events, i.e., a biomarker's trajectory is directly informative about the time to event. In this scenario, separate modeling of the survival outcome and the longitudinal processes may overlook the underlying association and lead to biased inference.

The goal of this research is to identify the optimal outcome measures for enriching an MCI treatment study population with subjects who are most likely to progress over time. Current study designs have become reliant on biomarkers at baseline as a strategy for enriching with decliners, but it remains to be seen whether this strategy will be effective. Incorporation of longitudinal data for subject selection is plausible, and some adaptive design studies have begun to explore this strategy [16–18]. However, the comparative predictive value of longitudinal clinical and imaging data has not been previously reported. In this paper, instead of considering the conversion of MCI to AD as a binary response, we assessed the ability of various measures to predict time from study entry to AD conversion (first occurrence) for MCI patients using joint modeling of longitudinal and time-to-event data [19,20]. The joint model analyzed these two types of outcomes simultaneously and was able to give more accurate parameter estimation and smaller standard errors which in turn yield greater statistical power. The specific measures chosen for comparison in this study covered the domains of clinical measures, neuropsychological assessments, neuroimaging, and functional and behavioral assessments. Relevant demographic and genetic variables (i.e., age, gender, education and *APOE* genotype) were employed as covariates given their potential effects on disease progression in AD [9].

2. Materials and Methods

2.1. Study design and participants

Data used in this analysis were obtained from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1) study (http://adni.loni.ucla.edu), which investigates the progression of Alzheimer's disease using serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and various clinical and neurocognitive

measures. Detailed information regarding the ADNI study procedures, including participant inclusion and exclusion criteria and complete study protocol can be found at http://www.adni-info.org. The data are publically available at http://ida.loni.ucla.edu and were downloaded on December 1, 2015.

This analysis included 384 patients with amnestic MCI at baseline evaluation who had at least one follow-up visit. Criteria for MCI were the same as defined by Petersen et al. [1]: a memory complaint that had objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a Folstein Mini-Mental State Examination score (MMSE) of 24–30, Clinical Dementia Rating (CDR) equal to 0.5, absence of significant levels of impairment in other cognitive domains, and essentially preserved activities of daily living. All subjects were given a written informed consent at the time of enrollment, and the study has been approved by the local institutional review board at all participating sites.

2.2. Measures

The ADNI study collected a broad range of clinical and biological data about patients. We first reviewed the literature and identified 33 measures, based on their availability in the ADNI dataset and sensitivity to detect conversion from MCI to AD in prior studies. As part of the ADNI-1, subjects were assessed at baseline, 6, 12, 18, 24 and 36 months, and continued follow-ups were conducted annually as part of the ADNI-2. All potential predictor measures were collected at multiple time points during the follow-up period. We did not consider the domains of cerebrospinal fluid (CSF) biomarkers, because it was collected in a small subset of ADIN-1 subjects at baseline and 12^{th} month only.

2.2.1. Neuropsychological assessment—Measurements in the neuropsychological domain included Alzheimer Disease Assessment Scale–Cognitive (ADAS-Cog), which assesses written and verbal responses of subjects that are related to fundamental cognitive functions. The total score is reported as a composite score of 11 or expanded to 13 items and ranges from 0 to 70 or 85, with a higher score indicating poor cognitive function. Other measures of verbal memory included were the Rey Auditory Verbal Learning Test (RAVLT immediate, RAVLT learning, RAVLT forgetting), the Mini Mental State Examination (MMSE; 11 questions with scores range from 0 to 30 and lower scores reflect severer cognitive impairment), Montreal Cognitive Assessment (MoCA; a 30-point test assesses different cognitive domains), and CDR Sum of Boxes (CDR-SB; sum of box method to stage severity of dementia with range from 0 to 18).

2.2.2. Functional and behavioral assessment—Variables included Functional Assessment Questionnaire (FAQ; 10 items with scores range from 0 to 30, with higher scores reflecting greater functional dependence), Everyday Cognition by the patient (ECogPt) and Everyday Cognition by the patient's study partner (ECogSP), which assesses participant's capability of performing normal everyday tasks in multiple domains (Memory, Language, Visuospatial Abilities, Planning, Organization, Divided Attention, and Total score).

2.2.3. Neuroimaging—Neuroimaging measures were PET imaging results including FDG-PET, PIB, and AV45, and MRI volumetric data of Ventricles, Hippocampus, Whole Brain, Entorhinal, Fusiform gyrus, Middle temporal gyrus (MidTemp), and intracerebral volume (ICV). The analyzed data from previous studies [21–24] were used. FDG-PET was represented as a sum of mean glucose metabolism uptake in regions of angular (right and left), temporal (right and left), and posterior cingulate [21]. PIB was the average of standardized uptake value (SUVR) of frontal cortex, anterior cingulate, precuneus cortex, and parietal cortex [22]. AV45 was the average of florbetapir SUVR of frontal, anterior and posterior cingulate, lateral parietal, and lateral temporal cortex [23]. The detailed protocol of ADNI PET data acquisition and processing are available at http://adni.loni.usc.edu/data-samples/pet/. The MRI data were acquired on 1.5T or 3T MRI scanners, and volumes of the region of interests (ROIs) were reconstructed with the *Freesurfer* [24].

2.3. Statistical analyses

The markers in this analysis were collected from participants at multiple time points during the follow-up period and were hypothesized to be related to AD progression-the event of interest. When the value of a marker at a time point is affected by the occurrence of an event at that time point, the longitudinal marker is an endogenous time-dependent covariate. However, the Cox model and its extensions cannot properly handle endogenous covariates [25]. We simultaneously modeled time-to-dementia as well as longitudinal change in the aforementioned neuro-psychological, neuro-imaging or functional/behavioral variables, using joint modelling for longitudinal and survival data. A joint model consisted of two sub-models: the longitudinal sub-model and the survival sub-model. The longitudinal sub-model allowed us to describe the evolution of a repeated measure over time, while adjusting for age at baseline and presence of apolipoprotein E (*APOE*) ε4 allele. A random intercept and a random slope of time were also included in the sub-model to capture the between subject variation. We assumed linear trajectories for the markers, because the longitudinal measures under consideration did not display highly non-linearity in the trajectories before their AD conversion (Figure 1 and 2). However, in a different setting where patients could have highly non-linear evolution, spline could be implemented in the longitudinal model to account for the nonlinear trajectories of measures. The survival time (in years) was defined as from the baseline visit date to AD conversion or censoring. Although certain participants were continued followed after the event of interest in the original study, we excluded the visits and measurements after AD conversion from this analysis. The survival sub-model took the form of a proportional hazards model with baseline covariates such as gender, age at baseline, presence of the *APOE* ε4 allele, years of education, and one of the longitudinal measures. An association parameter (α) linked the two sub-models, assuming the hazard was dependent on the longitudinal measure through its current value.

Suppose $y_i(t_{ij})$ were the observations of one of the longitudinal measurements for the ith person ($i = 1, \ldots, N$) at the jth time point ($j = 1, \ldots, n_i$), t_{ij}. The joint model was represented as

$$y_i(t_{ij}) = m_i(t_{ij}) + \varepsilon_i(t_{ij}), \text{ where}$$
$$m_i(t_{ij}) = \beta_0 + \beta_1\, t_{ij} + \beta_2\, baselineAge_i + \beta_3 i.APOE\varepsilon 4_i + b_{0i} + b_{1i}\, t_{ij}, \text{ and}$$
$$h_i(t) = h_0(t)\, exp\{\gamma_1\, gender_i + \gamma_2\, baselineAge_i + \gamma_3\, education_i + \gamma_4\, i.APOE\varepsilon 4_i + \alpha m_i(t)\}.$$

The parameter b_{0i} was the random intercept, b_{1i} was the random slope indicating subject-specific change rate of the measure, and $\varepsilon_i(t_{ij})$ was the measurement error. A significant α indicated a strong association between the longitudinal measure and time to AD conversion. The joint model was reduced to separate models if $\alpha = 0$, and the advantage of joint model disappeared. The quantity $exp(\alpha)$ was the hazard ratio (HR; inverse hazard ratio HR^{-1} was used when the α estimate was negative) for a one-unit increase in the trajectory $m_i(t)$, at time t. Specifically, a one-unit increase in trajectory increased the hazard by $exp(\alpha)$ times. To facilitate the comparison of the association parameter among markers, each maker was scaled to zero-mean and unit variance using the mean and standard deviation (SD) among all the participants and all the time points. For comparison, we also fitted a cross-sectional proportional hazards model (Cox model) that only incorporated the baseline measure in the prediction. The cross-sectional Cox model was represented as

$$h_i(t) = h_0(t)\, exp\{\gamma_1\, gender_i + \gamma_2\, baselineAge_i + \gamma_3\, education_i + \gamma_4\, i.APOE\varepsilon 4_i + \alpha y_{i1}\},$$

where $h_0(t)$ was the baseline hazard function and y_{i1} was the measure taken at the baseline visit. The parameter α in the Cox model quantified the association between the baseline measurement and the event hazard. We refer the readers to [26] for an introductory overview on joint modeling and the comparison with Cox model. For consistency, we scaled each marker at baseline to zero-mean and unit variance.

We also assessed how well these measures could discriminate between MCI patients who progressed to AD and those who had a stable status. We calculated time-dependent areas under the ROC curves (AUCs) to assess the performance of the longitudinal marker at different time points over the follow-up period. We also computed the dynamic discrimination index (DDI) [27], which summarized the discrimination power of the measure over the whole follow-up period for a Δt ahead prediction, using a weighted average of AUCs. In general, higher AUCs and DDI indicate higher discrimination of the models. We computed the probabilities of conversion to probable AD in the time frame $(t, t + \Delta t]$, which meant using all measures of subject survived till time t to perform a Δt ahead prediction. We selected t at 12^{th}, 18^{th}, and 24^{th} month, and Δt as 6 and 12 months.

To avoid overestimation of the predictive performance of the markers [28], we conducted a k-fold cross validation. The total sample of the MCI patients was randomly broken into k subgroups of approximately equal sizes. The analysis was repeated k times with one subset being left out as the test set and the others being used as the training set in each analysis. Parameter estimates of the joint model were derived from the training set and applied to the test set. Predictive accuracies were then computed by averaging the k separate analyses. We used k as 6 to have about 320 subjects in the training set and 64 subjects in the test set, which was considered necessary for power and allowed for a reasonable number of

validations. All the analyses were performed using R (version 3·2·1). Cross-sectional Cox modeling and proportionality testing were conducted using the survival package. The Joint modeling and time- dependent AUCs calculation were achieved using the JM package [29].

3. Results

The demographic characteristics of the study population are shown in Table 1. Participants were followed up for a mean of 3.2 years (SD 2.6; range 0.4–9.3 years) before conversion to AD or censoring. The average age at baseline was 74.7, 37.5% were women and a 15.6 years average education length. More than 54.2% of subjects had one or more *APOE* ε4 alleles. Among the 384 MCI patients, 200 patients converted to AD over a mean follow-up period of 2.3 years. 184 patients had stable MCI, of which 77 had less than 3 years of follow-up while 107 were followed for at least 3 years. 23% subjects had only one follow-up visit.

Table 2 shows the results of two models for each measure. We conducted the Z test of the null hypothesis in which the association parameter was zero (no association between maker and time to AD conversion). The HR was the primary effect size, and the markers were ranked based on the absolute Z value of the association parameter α from the longitudinal prediction model. The column of the association parameter for the cross-sectional Cox model indicates that the baseline information was a significant predictor of the hazard of AD progression for 19 of the 33 measures. The majority of the association parameters in the longitudinal model were larger (in absolute value) than their counterparts in the cross-sectional Cox model, where 23 out of 33 measures were significantly predictors of AD conversion. The longitudinal measures of ECogSP (in the domains of language, planning and visuospatial abilities) and RAVLT forgetting were significant predictors, although their baseline measures were not significant in the cross-sectional Cox model. Thus, prediction of AD progression based on both baseline and longitudinal changes was stronger than prediction based only on baseline information. Based on the results of the joint models, the strongest predictors were Alzheimer's Disease Assessment Scale test (ADAS-Cog 13, ADAS-Cog 11), followed by RAVLT immediate, FAQ and Middle temporal gyrus volume. Specifically, an increase of one SD (7.7 units) in trajectory of ADAS-Cog 13 score increases the hazard of AD conversion by 2.92 times (95% CI 2.33–3.66), a decrease of one SD (10.6 units) in trajectory of RAVLT immediate recall increases hazard by 3.16 times (95% CI 2.41–4.15), an increase of one SD (5.2 units) in trajectory of FAQ score increases hazard of AD conversion by 1.95 times (95% CI 1.64–2.34), and a reduction of one SD (2851 mm^3) in middle trajectory of temporal gyrus volume increases hazard by 1.98 times (95% CI 1.65–2.37).

Figure 1 shows individual empirical curves and fitted spline curves before AD conversion for the participants who progressed to AD during the study, for ADAS-Cog 13, ADAS-Cog 11, CDR-SB and FDG-PET, respectively. Dashed lines are individual empirical data and solid lines are cubic spline curves (shading shows 95% CIs). The vertical line in each panel denotes the year of AD diagnosis (set to year 0). The figure shows that all measures deteriorated as AD progressed. Figure 2 shows the trajectories and fitted spline curves for participants who progressed and those who did not progress to AD, for ADAS-Cog 13, ADAS-Cog 11, CDR-SB and FDG-PET, respectively. Only measurements before AD

conversion or censoring are plotted on the figure. Participants who progressed to AD and those who did not progressed to AD during the study can be clearly distinguished by each of these measures.

Table 3 compares the discriminative capability of the top 10 strongest predictors by calculating the time-dependent AUCs at 12^{th}, 18^{th}, and 24^{th} month. Different from just using baseline predictors, the prediction in joint model was based on accumulating evidence. Specifically, the values in the first column in Table 3 evaluated the performance of using all previous observations of the remaining MCI patients (those who had not progress to AD) at time 12^{th} month (sample size $n = 315$) to predict their disease status between 12^{th} and 18^{th} month. The DDI summarizes the discrimination power of the marker to predict the patients' disease status in the next 6 or 12 months. Among the predictors, ADAS-Cog 13 had the best discrimination performance with AUCs ranging from 0.740 to 0.859 for all combinations of t and Δt, and DDI being 0.789 and 0.785 for Δt as 6 and 12 months, respectively. In general, cognitive and functional markers (ADAS, Auditory Verbal Learning Test, FAQ and MMSE) have higher AUCs and DDI than those of imaging markers, indicating that cognitive measures may be more useful in predicting risk of AD conversion within a few years among MCI patients.

4. Discussion

In this paper, we used comprehensive longitudinal assessments to predict dementia in Alzheimer's disease in a manner that has not been accomplished by prior studies. By accounting for dependent terminal events, the joint models of longitudinal change and time to AD conversion identified several significant predictors. The strongest predictors are in the cognitive domain (ADAS-Cog, RAVLT), functional domain (FAQ), and neuroimaging domain (middle temporal gyrus and hippocampal volume). These findings are consistent with reports in the literature [3,4,6–9].

Our study has also consolidated the findings in Fleisher, et al. [30] in the sense that common cognitive measures could provide more accurate prediction regarding AD conversion than volumetric MRI measures by evaluating the discriminative capability of the measures at different time points. In a large meta-analysis which did not include ADNI data, baseline cognitive measures were demonstrated as better predictors of AD conversion than brain volumetric markers [31]. Thus, with consideration of the comparative economy of cognitive measures, in expense and time, these measures should still be the gold standard for clinical assessment of conversion from MCI to AD. In addition, we note that different markers may show different predictive values at different times in disease progression. This has been reflected in the different changes of AUCs with the passage of time. The cognitive measures such as ADAS-Cog retain a moderate discriminative capability even in the later phrase of disease process while neuroimaging measures (volumetric MRI, PET) become less useful as time passes. This may explain why volumetric changes on MRI were reported to be better predictors than cognitive measures among cognitively normal individuals [32]. A similar point was also made in the literature [33,34]. Our analyses controlled for the presence of *APOE* and demographic variables that have been associated with cognitive decline or the likelihood of developing AD. One caveat in our study is that some neuropsychological tests

and clinical measures, such as CDR Sum of Boxes, may be used in the diagnostic process of AD. However, diagnoses are based, in various weight, on clinical history, laboratory data, and a full battery of tests which include some of the selected measures. It is also known that how far someone has progressed on a staging or cognitive measure predicts how fast they decline. So it is reasonable to explore selected measures as predictors in the joint models.

There are several limitations in our study. First, not all ADNI-1 participants underwent all measurements examinations, especially PET imaging and Everyday Cognition. The differences in sample sizes, particularly the smaller sample of FDG-PET and PIB-PET, may limit our ability to compare their predictive capabilities. However, this did not affect our conclusion on the other markers. Second, while each measure independently showed promise in predicting disease progression in our study, many recent researchers have shown interest in examining biomarker combinations as predictors for AD conversion [35–37]. The joint model adopted in present analysis can only handle a single longitudinal outcome, but can be extended to incorporate multivariate longitudinal measures as proposed in He, et al. [38]. The general idea is to introduce a continuous latent variable to represent patients' underlying disease severity. The observed longitudinal markers can be modeled as measurements of the latent variable using a multilevel item response theory sub-model and the time-to-event data are modeled using a Cox proportional hazard sub-model. Because all outcomes share the same latent variable, the dimensionality of the data can be reduced and fewer parameters are needed. Wang, et al. [39] proposed a prediction framework for multiple longitudinal measures and event time data based on the method. Simultaneous modeling of multiple longitudinal outcomes in joint models may substantially enhance the predictive ability of a joint model, and help to identifying the optimal combination of measures in determining the risk of incident AD dementia in MCI patients. Moreover, rather than using the diagnoses assigned by ADNI, which has been shown to produce a high rate of false positive diagnostic errors, the new approach for staging preclinical AD [40] would sharpen our model to identify early predictors. Last, the ADNI cohort is a convenience sample rather than an epidemiologic cohort, it is likely to result in recruiting more impaired subjects. However, this study focus on MCI population, may be less prone to selection bias than the larger ADNI study population. The cross-validation used in the analysis was an internal validation, and external validation with an independent data set could further consolidate our findings.

In summary, our study was the first attempt to comprehensively and systematically evaluate the predictive ability of markers for AD conversion under the joint model framework, which includes both baseline measures and changes in these measures over time. The sample from ADNI that we used was large, and the data were collected uniformly, rigorously and on a broad range of measures. We demonstrated that cognitive measures were consistently significant and generally stronger predictors than imaging measures, with ADAS-Cog 13 as the optimal predictor. Moreover, the measures identified as strong predictors in this study along with each joint model can be used for subject specific prediction. Such individualized risk prediction can help personalize screening strategies and/or guide the initiation of treatment among MCI patients or subject selection for clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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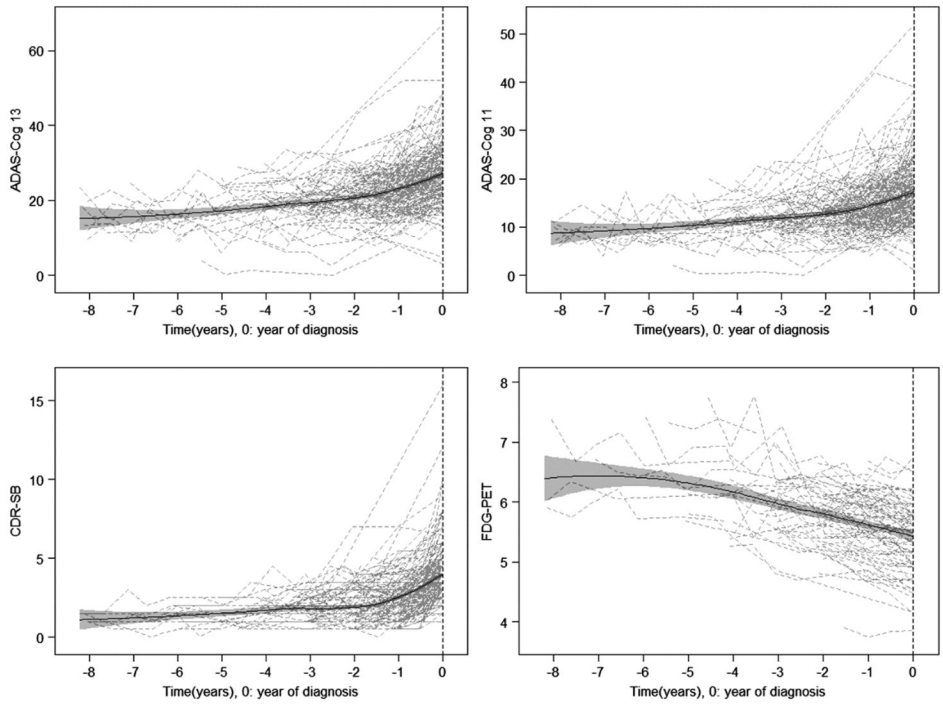

Figure 1. Trajectories of ADAS-Cog 13, ADAS-Cog 11, CDR-SB and FDG-PET before AD conversion for the 200 participants who progressed to AD during the study

Dashed lines (light gray) are individual empirical data solid lines are cubic spline curves (shading shows 95% CIs). The vertical line in each panel denotes year of AD diagnosis (set to year 0). ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale test. CDR-SB = Clinical Dementia Rating Sum of Boxes. FDG-PET = Sum of mean glucose metabolism uptake in regions of angular, temporal, and posterior cingulate.

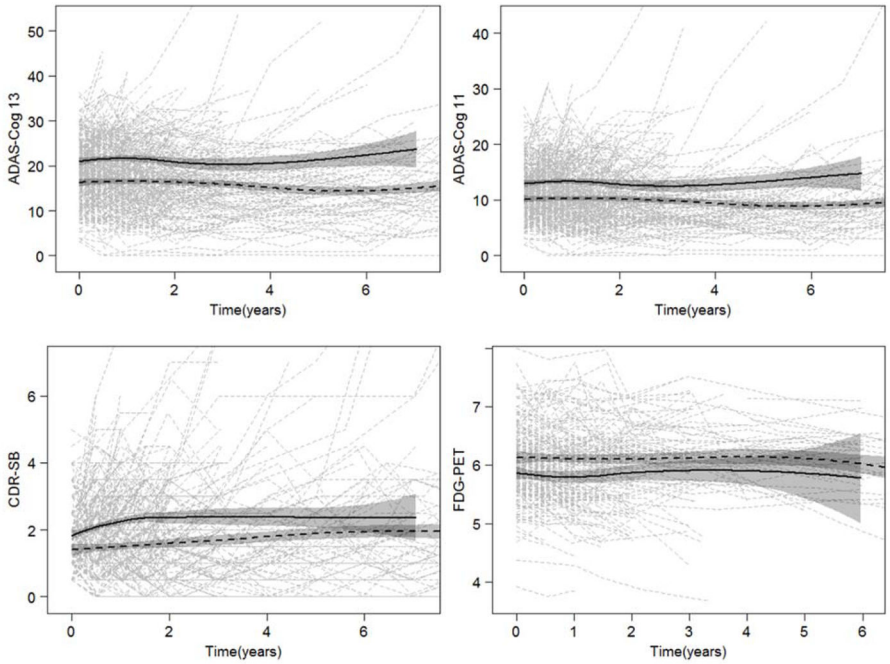

Figure 2. Trajectories of ADAS-Cog 13, ADAS-Cog 11, CDR-SB and FDG-PET for all participants

Dashed lines (light gray) are individual empirical data. The solid lines represent participants converted to AD during the study and the wide dashed lines represent the participants not converted to AD during the study (shading shows 95% CIs). The two groups can be clearly distinguished by each of these measures. 0 denotes year of entry the study. ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale test. CDR-SB = Clinical Dementia Rating Sum of Boxes. FDG-PET = Sum of mean glucose metabolism uptake in regions of angular, temporal, and posterior cingulate

Table 1

Baseline characteristics of ADNI-1 participants with mild cognitive impairment (MCI)

	Progressed to AD during the study (n = 200)	Did not progress to AD during the study (n = 184)	Combined (n = 384)
Women	75 (37.50%) *	62 (33.50%)	137 (35.7%)
Age (years)	74.44 (7.09)	75.03 (7.55)	74.71 (7.31)
APOE4 present	127 (63.50%)	81 (44.00%)	208 (54.16%)
Education (years)	15.82 (2.86)	15.33 (3.19)	15.58 (3.03)
Time in study (years)	2.25 (1.74)	4.24 (2.91)	3.20 (2.57)

* Data are mean (SD) or n (%)

Table 2

Prediction of risk of AD progression: model results (controlled for age, *APOE* in the longitudinal model and controlled for age, gender, years of education and *APOE* in the survival model)

				Cross-sectional prediction (Cox Model)			Longitudinal prediction (Joint Model)		
Variable*	**Participants**	**Observations**	**Events†**	**α**	**Z value**	**HR‡ or HR^{-1} (95% CI)**	**α**	**Z value**	**HR‡ or HR^{-1} (95% CI)**
ADAS-Cog 13	384	1872	200	0.95	9.08	2.57 (2.10 – 3.16)	1.07	9.33	2.92 (2.33 – 3.66)
ADAS-Cog 11	384	1890	200	0.81	8.18	2.25 (1.85 – 2.74)	0.92	8.40	2.52 (2.03 – 3.12)
RAVLT.immediate	384	1883	200	−0.85	−8.26	2.34 (1.92–2.85)	−1.15	−8.32	3.16 (2.41 – 4.15)
FAQ	384	1895	200	0.59	8.06	1.80 (1.56 – 2.07)	0.67	7.38	1.95 (1.64 – 2.34)
MidTemp	362	1290	184	−0.64	−7.22	1.90 (1.59 – 2.26)	−0.68	−7.31	1.96 (1.65 – 2.37)
RAVLT.learning	384	1883	200	−0.37	−4.61	1.44 (1.23 – 1.68)	−1.24	−6.45	3.47 (2.38 – 5.06)
MMSE	384	1888	200	−0.57	−4.78	1.76 (1.40 – 2.23)	−0.58	−6.43	1.79 (1.50 – 2.13)
Hippocampus	362	1296	184	−0.60	−6.49	1.83 (1.52 – 2.20)	−0.60	−6.30	1.82 (1.51 – 2.19)
CDR-SB	384	1892	200	0.75	6.08	2.11 (1.66 – 2.69)	0.66	6.30	1.93 (1.57 – 2.37)
FDG-PET	220	905	100	−0.56	−4.65	1.76 (1.38 – 2.22)	−0.74	−6.08	2.11 (1.66 – 2.68)
Entorhinal	362	1290	184	−0.49	−5.62	1.64 (1.38 – 1.95)	−0.61	−6.00	1.84 (1.51 – 2.25)
Fusiform	362	1290	184	−0.43	−4.83	1.53 (1.29 – 2.26)	−0.50	−5.33	1.64 (1.37 – 1.98)
EcogSPTotal	79	282	13	1.01	2.85	2.75 (1.37 – 5.51)	1.34	3.24	3.83 (1.70 – 8.63)
WholeBrain	383	1612	199	−0.33	−3.46	1.40 (1.16 – 1.69)	−0.32	−3.21	1.38 (1.13 – 1.68)
EcogSPMem	80	283	13	0.99	3.02	2.70 (1.42 – 5.14)	1.37	3.14	3.93 (1.67 – 9.22)
EcogSPLang	80	285	13	0.55	1.82	1.73 (0.96 – 3.11)	1.11	2.96	3.03 (1.46 – 6.32)
EcogSPDivatt	79	264	13	0.97	2.59	2.63 (1.27 – 5.49)	1.54	2.93	4.67 (1.67 – 13.09)
EcogSPOrgan	78	273	13	0.72	2.29	2.06 (1.11 – 3.81)	0.98	2.85	2.66 (1.36 – 5.22)
EcogSPPlan	79	277	13	0.49	1.45	1.64 (0.84 – 3.20)	1.20	2.66	3.33 (1.37 – 8.08)
RAVLT.forgetting	384	1878	200	0.12	1.62	1.13 (0.97 – 1.30)	0.45	2.65	1.57 (1.13 – 2.20)
EcogSPVisspat	77	274	12	0.64	1.92	1.90 (0.99 – 3.66)	0.93	2.49	2.53 (1.22 – 5.25)
Ventricles	383	1597	199	0.20	2.57	1.22 (1.05 – 1.42)	0.18	2.37	1.19 (1.03 – 1.38)
AV45-PET	58	104	10	0.74	2.00	2.09 (1.02 – 4.31)	0.76	2.01	2.14 (1.02 – 4.48)
EcogPtOrgan	79	285	13	0.44	1.81	1.56 (0.96 – 2.52)	0.65	1.95	1.91 (1.00 – 3.68)
EcogPtMem	80	290	13	0.48	1.81	1.61 (0.96 – 2.70)	0.71	1.92	2.03 (0.99 – 4.16)
EcogPtTotal	80	290	13	0.34	1.35	1.41 (0.86 – 2.33)	0.52	1.66	1.69 (0.91 – 3.13)

				Cross-sectional prediction (Cox Model)			Longitudinal prediction (Joint Model)		
Variable*	**Participants**	**Observations**	**Events†**	**α**	**Z value**	**HR‡ or HR^{-1} (95% CI)**	**α**	**Z value**	**HR‡ or HR^{-1} (95% CI)**
EcogPtDivatt	80	289	13	0.21	0.80	1.23 (0.74 – 2.04)	0.47	1.36	1.61 (0.81 – 3.17)
MOCA	77	274	13	−0.22	−0.64	1.25 (0.63 – 2.46)	−0.50	−1.34	1.66 (0.79 – 3.46)
PIB-PET	60	113	27	0.24	1.05	1.27 (0.81 – 1.99)	0.32	1.31	1.37 (0.85 – 2.21)
EcogPtLang	80	289	13	0.26	0.94	1.30 (0.75 – 2.25)	0.39	1.08	1.48 (0.73 – 3.01)
EcogPtPlan	80	290	13	0.07	0.29	1.08 (0.65 – 1.77)	0.42	0.99	1.52 (0.66 – 3.48)
EcogPtVisspat	80	286	13	0.04	0.12	1.04 (0.56 – 1.93)	0.30	0.93	1.34 (0.72 – 2.50)
ICV	384	1632	200	0.01	0.10	1.01 (0.84 – 1.21)	0.00	0.05	1.00 (0.83 – 1.21)

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale - Cognitive Subscale test; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Assessment Questionnaire; MidTemp, Middle temporal gyrus; MMSE, Mini Mental State Examination; CDR-SB, Clinical Dementia Rating Sum of Boxes; FDG-PET, Sum of mean glucose metabolism uptake in regions of angular, temporal, and posterior cingulate; ECogPt, Everyday Cognition questionnaire filled out by the patient. ECogSP, Everyday Cognition questionnaire filled out by the patient's study partner; MOCA, Montreal Cognitive Assessment; ICV, Intracerebral volume.

*Measures are ranked by absolute Z-value for the association parameter (α) of the Joint Model.

†Events are the number of conversions to AD.

‡Hazard ratio (HR) or inverse hazard ratio (HR^{-1}) show the hazard for AD diagnosis associated with a difference of one SD in each measure.

Table 3

Areas under the ROC curve and estimated dynamic discrimination index *

$\Delta t^{\ddagger}$(month)		6			12		
$t^{\dagger}$ (month) (n)		12 (n = 315)	18 (n = 265)	24 (n = 217)	12 (n = 315)	18 (n = 265)	24 (n = 217)
ADAS-Cog 13	AUC	0.8	0.74	0.86	0.78	0.78	0.81
	DDI		0.79			0.79	
ADAS-Cog 11	AUC	0.79	0.72	0.86	0.76	0.77	0.79
	DDI		0.78			0.78	
RAVLT.Immediate	AUC	0.78	0.76	0.85	0.78	0.79	0.83
	DDI		0.78			0.76	
FAQ	AUC	0.79	0.74	0.81	0.78	0.75	0.77
	DDI		0.74			0.72	
MidTemp	AUC	0.71	0.73	0.71	0.74	0.72	0.68
	DDI		0.67			0.69	
RAVLT.Learning	AUC	0.74	0.69	0.78	0.72	0.71	0.73
	DDI		0.74			0.71	
MMSE	AUC	0.74	0.72	0.83	0.74	0.74	0.75
	DDI		0.75			0.72	
Hippocampus	AUC	0.73	0.66	0.74	0.7	0.71	0.69
	DDI		0.68			0.69	
CDR-SB	AUC	0.77	0.73	0.8	0.77	0.74	0.74
	DDI		0.73			0.72	
FDG-PET	AUC	0.76	0.68	0.77	0.72	0.7	0.68
	DDI		0.7			0.71	

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale - Cognitive Subscale test; RAVLT, Rey Auditory Verbal Learning Test; FAQ, Functional Assessment Questionnaire; MidTemp, Middle temporal gyrus; MMSE, Mini Mental State Examination; CDR-SB, Clinical Dementia Rating Sum of Boxes; FDG-PET, Sum of mean glucose metabolism uptake in regions of angular, temporal, and posterior cingulate.

[*] The top 10 strongest predictors. AUC is the area under the ROC curve and DDI is dynamic discrimination index. Higher value indicates higher discrimination capability.

[†] t is follow-up time, corresponding to different amounts of available longitudinal information. n is the remaining MCI patients at time t. Predictive utility is evaluated based on the longitudinal measure of these n patients observed before time t.

[‡] Δt is relevant time window, corresponding to different prediction intervals.

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