Psychiatry Research 291 (2020) 113201

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Predicting Alzheimer's disease based on survival data and longitudinally measured performance on cognitive and functional scales

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ARTICLE INFO

Keywords:
Alzheimer's disease
Joint modeling
Predictive performance
Primary screening

ABSTRACT

This study assessed how well longitudinally taken cognitive and functional scales from people with mild cognitive impairment (MCI) predict conversion to Alzheimer's disease (AD). Participants were individuals with baseline MCI from the Alzheimer's Disease Neuroimaging Initiative. Scales included the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) 11 and 13, the Mini Mental State Examination (MMSE), and the Functional Assessment Questionnaire (FAQ). A joint modelling approach compared performance on the four scales for dynamic prediction of risk for AD. The goodness of fit measures included log likelihood, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). The area under the curve (AUC) of the receiver operating characteristic assessed predictive accuracy. The parameter α in the ADAS-Cog11, ADAS-Cog13, MMSE, and FAQ joint models was statistically significant. Joint MMSE and FAQ models had better goodness of fit. FAQ had the best predictive accuracy. Cognitive and functional impairment assessment scales are strong screening predictors when repeated measures are available. They could be useful for predicting risk for AD in primary healthcare.

1. Introduction

As the most common type of dementia, Alzheimer's disease (AD) has become a major threat to the quality of life of older people (Hill et al., 2017). Mild cognitive impairment (MCI) is often considered a transitional stage before advancing to AD, and patients with MCI convert to AD with an annual progression rate ranging between 10% and 15%, which is much higher than the 1%–2% rate observed in the general population (Petersen, 2000; Zhai et al., 2016). Thus, patients with MCI are usually enrolled as the target population for early prognosis and evaluating interventions (Petersen et al., 1999).

Markers that signal MCI to AD transformation have been studied as a means to quantify disease progression, including neuropsychological assessments, clinical markers, and neuroimaging findings. Imaging techniques such as magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (PET) are expected to detect the development of neuropathological changes. Imaging technology is non-invasive, objective, and real-time, which provides the possibility of early diagnosis of AD (Teipel et al., 2015). Experts advocate that at least one neuroimaging examination is needed for a diagnosis of dementia, but frequent imaging examinations are not realistic for long-term monitoring of patients with MCI. And expensive high-tech machinery is largely unavailable to large portions of the population, especially in non-specialist settings. In addition to clinical and imaging, biosensors and biomarkers are promising diagnostic approaches. AD biomarkers present in CSF, in plasma and in genetic, which are important basis for early diagnosis, course monitoring, guiding treatment. Biosensors (using optical, electrochemical and colorimetric techniques) are presented as promising approaches for simple, rapid and low cost diagnosis of AD (Brazaca et al., 2020). However, they also have some limits to expect to be solved, such as lack of specificity, high variability of test results and difficulty in determining uniform thresholds (Carrillo et al., 2013; Hepp et al., 2016). Data from some of these technologies can be collected only in tertiary or specialized medical centers and are not suitable for achieving large-scale benefits. For the majority of patients with MCI, detecting disease

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at:http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

https://doi.org/10.1016/j.psychres.2020.113201
Received 9 March 2020; Received in revised form 4 June 2020; Accepted 5 June 2020
Available online 08 June 2020
0165-1781/

progression can be achieved through longitudinal long-term assessments with standardized cognitive scales, which is simpler and more practical, especially in the elderly at the community level or in areas with poor medical conditions. More comprehensive examinations are necessary for high reliability of results when diagnosing disease or following up to monitor disease progression.

Considering the dynamic and multidimensional nature of the aging process, neuropsychological and functional test batteries can identify and track subtle cognitive changes that occur in the prodromal phase of the disease (Chapman et al., 2011). Neuropsychological tests at different time points can more accurately reflect actual cognitive and functional abilities than baseline measurements (Xue et al., 2017). The joint model can capture trajectory and predictive performance of longitudinal markers. Furthermore, dynamic individual predictions of an event of interest can be easily obtained from a joint model (Proust-Lima and Taylor, 2009; Rizopoulos, 2011; Sène et al., 2013). As such, risk predictions for events of interest can be adjusted based on individual developmental trajectories. Predicting conversion from MCI to AD using information from such tests may assist primary healthcare physicians with limited resources to monitor cognitive impairments effectively.

In recent years, dementia research usually includes longitudinal data generated by repeated measures of multiple indicators such as cognitive function and survival data that record the time that dementia or death occur. Longitudinal data analysis can predict the trajectory of future measurements or clinical scores in patients with MCI (Henderson et al., 2000; Proust-Lima et al., 2014), while failure to take into account dependent terminal events in that a biomarker's trajectory is directly informative about the time to event (Lo et al., 2011; Zhang and Shen, 2012). This deficiency is potentially leading to biased estimation. For survival data analysis, most risk prediction studies (Rizopoulos, 2011; Sène et al., 2013) use Cox regression models based on baseline measurements. This approach implicitly assumes that the predictors stay constant for the length of the study, but this is unlikely to be true over an extended period of years. Thus, more complex statistical methods are needed to enable both longitudinal repeated biomarker measurements and survival processes to be modelled together while taking account of their relationship.

Therefore, in this study we joint modeled longitudinal measurements and survival data from different scales to explore the relationship with AD and to assess their ability to predict transition to AD.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Krishnan et al., 2005) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Michael W. Weiner. ADNI enrolls participants between the ages of 55 and 90 who are recruited at 57 sites in the United States and Canada. After obtaining informed consent, participants undergo a series of initial tests that are repeated at intervals over subsequent years. The primary goal of the ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

Participants were included in the current study if they had diagnosis of MCI at baseline, including those who developed AD during the follow-up period from 2005-2017. The inclusion and exclusion criteria were as follows. Inclusion criteria: 1) MMSE score range between 24 and 30. 2) Geriatric Depression Scale score less than or equal to 5. 3) Age 65 years or above. 4) Medication stable. 5) Good general health. Exclusion criteria: 1) Meet the DSM-IV criteria for Dementia. 2) Significant neurological or psychiatric illness other than AD. 3) Significant unstable systematic illness or organ failure. At 6 month intervals participants had been administered a multi-test cognitive battery in person or contacted by telephone and the patients were followed up at least once. At the entry visit into ADNI, cohort subjects received an initial diagnosis. General background and basic clinical data were obtained from the baseline visit.

2.2. Measures

We combined the key cognitive and functional scales collected by the ADNI with previous studies and decided on the following scales (Kueper et al., 2018; Li et al., 2017; Wessels et al., 2015). Measurements in the neuropsychological domain included the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) (Mohs et al., 1997; Rosen et al., 1984) and the Mini Mental State Examination (MMSE) (Folstein et al., 1975). The ADAS-Cog is used to evaluate the cognitive characteristics of AD and as the criterion to measure the results of AD treatment trials. The total score is reported as a composite score of 11 or expanded to 13 items and ranges from 0 to 70 (ADAS-Cog 11) (Rosen et al., 1984) or from 0 to 85 (ADAS-Cog13) (Mohs et al., 1997), with higher scores indicating poorer cognitive function. The MMSE includes 11 questions with scores ranging from 0 to 30, with lower scores reflecting more severe cognitive impairment. Social activity ability was evaluated by the Functional Assessment Questionnaire (FAQ) (Rozzini et al., 2008). The FAQ assesses patient ability to perform 10 items in daily life. Scores range from 0 to 30, with higher scores reflecting greater functional dependence. Demographic data and apolipoprotein E (ApoE) ε4 allele status (present or not) were also obtained at the baseline visit.

2.3. Statistical analyses

Except for baseline age and assessment scores, which were continuous, other covariates in the model were re-coded as binary variables to enable estimation of class-specific parameters. These included sex (1: Male, 2: Female), educational level (1: high school and below, 2: college and above), marital status (1: single (unmarried, divorced, separated, or widowed), 2: married), ApoE ε4 (1: absent, 2: present) and diagnosis status (1: MCI, 2: AD). Continuous variables are shown as mean (SD).

Cognitive and functional measures were collected at multiple time points (at 6 month intervals) during the follow-up period and were hypothesized to be related to the end-point event (progression to AD). Joint models that take into accounts both patient characteristics and longitudinal measurements were developed and assessed the predictive power.

A joint model consists of two sub-models: the longitudinal sub-model and the survival sub-model. The longitudinal sub-model is a linear mixed-effect model (Laird and Ware, 1982) that describes the evolution of cognitive and social functions over time, while adjusting for covariates such as age at baseline, sex, educational level, marital status, and presence of ApoE ε4. A random intercept and a random slope of time are also included in the longitudinal sub-model to capture participant variation. The survival sub-model takes the form of a Cox proportional hazards model (Andersen et al., 1982; Fleming and Harrington, 2011) with baseline covariates including age, sex, ApoE ε4, educational level, and one of the longitudinal measures. The survival time (in months) is defined as the time between the baseline visit and AD conversion. The parameter α in the Cox model links the two sub-models and quantifies the association between the longitudinal measurements and the risk of AD conversion.

The parameter estimation of the joint model uses the maximum likelihood estimates method (Rizopoulos, 2010; Wulfsohn and Tsiatis, 1997). We used logarithmic likelihood function values, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) to assess the goodness of fit of the model. The smaller the AIC and BIC values, the larger the logarithmic likelihood function

values and thus the better the model fitting. In addition, individual risk prediction of AD computed for a new participant given their biomarker history can be obtained from the joint model. The first 6 time points (the data of the first 36 months) were used as the training set, and the data of the later time points were used as the test set. The parameter estimation of the joint model was derived from the training set and applied to the test set. The area under the receiver operator characteristic (ROC) curve (AUC) in the time frame $(t, t + \Delta t)$ was calculated to assess the discriminative capability of the four longitudinal markers for AD conversion (Li et al., 2017). We selected t at 42nd, 48th, 54th, and 60th month, and Δt as 9 and 18 months. An AUC of 0.5 indicates no discrimination between cases and controls, whereas an AUC of 1.0 indicates perfect discrimination (Bansal and Heagerty, 2019).

Analyses were performed using the package "JM" in R, version 3.5.1. The hazard ratio (HR) and its 95% confidence interval (CI) are reported. $P < 0.05$ was considered to be significant.

3. Results

A total number of 501 participants with MCI at baseline participated and 277 (55.3%) developed AD during the follow-up period. Participants were followed up for a mean of 46.5 ± 32.7 months (range 6–120 months) before conversion to AD or censoring. The average (± SD) scores for the ADAS-Cog11, ADAS-Cog13, MMSE, and FAQ were 14.15 ± 6.35, 22.38 ± 8.37, 25.55 ± 3.27, and 7.23 ± 6.43, respectively. Table 1 shows the demographic characteristics of the study population. Fig. 1 presents cognitive and functional aging is a highly complex, dynamic and multidimensional process.

3.1. Joint model results for the four assessment scales

The results of the joint model with repeated measurements of the ADAS-Cog11, ADAS-Cog13, MMSE, and FAQ score as longitudinal markers are shown in Table 2. In the joint model, the longitudinal sub-model included follow-up time, educational level, sex, marital status, baseline age, and ApoE ε4 gene status. The survival sub-model included sex, ApoE ε4 status, educational level, and one of the longitudinal markers.

The effects of covariates can be explained by model parameter estimates. In the longitudinal part of the models, a significant effect of time on ADAS-Cog11, ADAS-Cog13, MMSE, and FAQ was observed during the study period ($P < 0.001$). Concurrently, the association between the four longitudinal markers and AD incidence were evaluated using the parameter α. The correlation parameter α in the four models indicated statistical significance ($P < 0.001$). We found increased risk of AD with higher scores on the ADAS-Cog11 (HR: 1.193; 95% CI: 1.159–1.228), ADAS-Cog13 (HR: 1.153; 95% CI: 1.128–1.178), MMSE (HR: 0.797; 95% CI: 0.766–0.829), and FAQ (HR: 1.181; 95% CI: 1.153–1.209).

Table 3 shows the goodness-of-fit test for the four models. The joint models based on repeated measurements of MMSE and FAQ scores as fitted better than the model for the other markers.

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

Characteristics	Mean (SD) or n (%)
Age, years	74.07 (7.39)
Sex	
Male	304 (60.7%)
Female	197(39.3%)
Educational level, years	15.86 (2.96)
Marital status	
Married	391 (78.0%)
Single	110 (22.0%)
ApoE ε4	
Present	221 (44.1%)
Absent	280 (55.9%)
Diagnosis status	
MCI	224 (44.7%)
AD	277 (55.3%)
ADAS-Cog11	14.15 (6.35)
ADAS-Cog13	22.38 (8.37)
MMSE	25.55 (3.27)
FAQ	7.23(6.43)

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale-Cognitive; MMSE, Mini-Mental State Examination; FAQ, Functional Activities Questionnaire; SD, standard deviation.

3.2. Predictive performance of different longitudinal markers

Table 4 compares prediction accuracy of four longitudinal markers at different times, indicating that all four longitudinal markers have moderate predictive ability. For example, in the first column of Table 4, we used all previous observations of the remaining patients with MCI (those who had not progressed to AD) at month 42 to predict their disease status between month 42 and 51.

Across the whole time of the analysis $(t, t+\Delta t)$, the prediction accuracy of the FAQ scale was the best, with AUCs ranging from 0.736 to 0.852. In addition, different markers showed different predictive values at varying time points during disease progression, which were also reflected in changes in the AUC over time. These results indicate that the FAQ still maintains moderate discriminatory ability.

4. Discussion

We used joint modeling to examine the association between variations in repeated longitudinal cognitive/functional measures and AD progression. The joint modeling analyses included both longitudinal and survival data, which allowed the dependency and correlation between longitudinal measures and event occurrence to be assessed. Moreover, it could consider problems such as measurement error, missing information, and random effects caused by individual differences.

From the α parameter in the joint model, we saw that the ability of the ADAS-Cog11, ADAS-Cog13, MMSE, and FAQ to predict the risk of conversion MCI to AD was statistically significant. Thus, cognitive decline and functional impairment (the predictors) over time may increase the risk of AD in patients with MCI. Furthermore, we compared the predictive performance (i.e., the AUC) of four longitudinal markers and found that the FAQ was the strongest predictor of conversion from MCI to AD, followed by the ADAS-Cog and the MMSE. Previous studies have shown that the FAQ can differentiate patients with MCI from those with AD with high discriminatory ability (Marshall et al., 2015; Teng et al., 2010), and the individual items can predict AD more sensitively. It may be that better daily activities and substantial social engagements stimulate blood circulation in the prefrontal cortex-striatum circuit, thereby improving cognitive function (Gill et al., 2011). FAQ is helpful to check whether the individual's neuropsychological symptoms are abnormal, such as delusion, excitement, abnormal motor function, etc. Individuals may experience steep functional declines in the immediate years post-diagnosis, which reflects the longitudinal dynamic change of FAQ (Jutkowitz et al., 2017). And minor interruptions in daily function can indicate later stages of disease progression in patients with MCI, so the FAQ is an essential tool for identify signs for alarm (Brown et al., 2011). It is worth noting that a quantitative metric threshold of functional decline to accurately separate MCI and AD has not been established. Solving this problem requires identifying potential biological mechanisms that cause disruptions in daily activities.

Fleisher et al. compared the predictive accuracy of cognitive measurements including ADAS-Cog and MMSE in predicting the progress of AD, and found that the accuracy was high (Fleisher et al., 2008). They

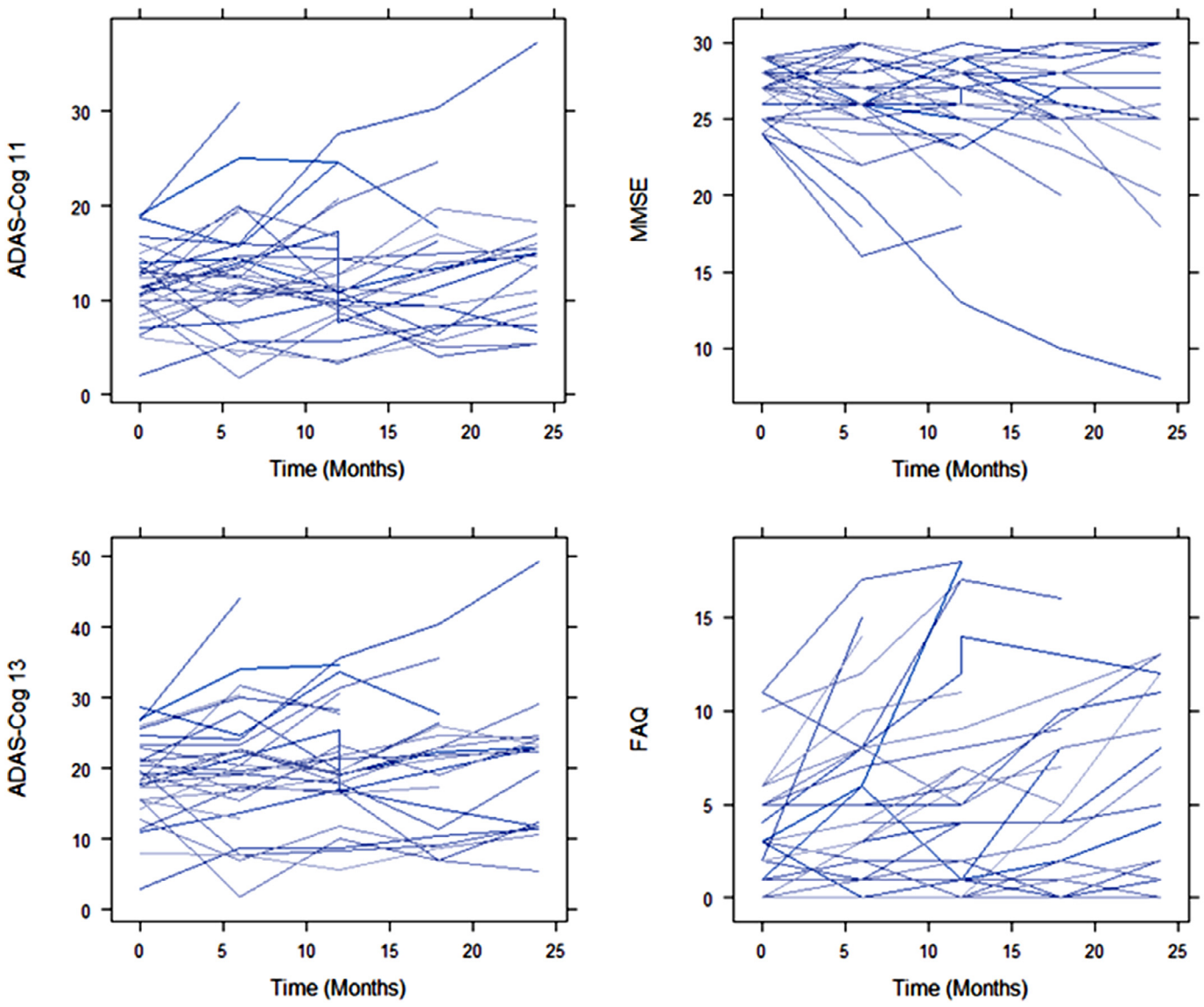

Fig. 1. Trajectories of ADAS-Cog 11, ADAS-Cog 13, MMSE and FAQ for 30 random participants

Table 2
Joint Model Results for the ADAS-Cog11, ADAS-Cog13, MMSE, and FAQ

Variable	ADAS-Cog11 Coefficient	*p*	ADAS-Cog13 Coefficient	*p*	MMSE Coefficient	*p*	FAQ Coefficient	*p*
Longitudinal sub-model								
Intercept	5.217	0.013*	9.640	0.001*	29.983	<0.001*	2.125	0.333
Follow-up time	0.116	<0.001*	0.166	<0.001*	-0.078	<0.001*	0.169	<0.001*
Educational level	-0.447	0.362	-1.073	0.127	0.518	0.014*	0.293	0.583
ApoE ε4	1.426	<0.001*	2.395	<0.001*	-0.382	0.023*	0.754	0.067
Sex	0.186	0.662	0.455	0.456	-0.389	0.032*	-0.221	0.619
Marital status	-1.570	0.002*	-2.318	0.001*	0.478	0.025*	-1.338	0.011*
Baseline age	0.087	0.001*	0.126	0.001*	-0.042	<0.001*	0.021	0.445
Survival sub-model								
Sex	0.965(0.737,1.264)	0.798	0.912(0.694,1.199)	0.509	0.905(0.691,1.185)	0.469	1.366(1.040,1.794)	0.025*
ApoE ε4	1.443(1.089,1.913)	0.011*	1.367(1.030,1.815)	0.031*	1.554(1.180,2.047)	0.002*	1.587(1.197,2.106)	0.001*
Educational level	1.212(0.849,1.730)	0.290	1.259(0.876,1.808)	0.213	1.100(0.782,1.544)	0.587	1.092(0.766,1.558)	0.625
α	1.193(1.159,1.228)	<0.001*	1.153(1.128,1.178)	<0.001*	0.797(0.766,0.829)	<0.001*	1.181(1.153,1.209)	<0.001*

For the Survival sub-model, the coefficient is hazard ratio.
* $p < 0.05$

Table 3
The goodness-of-fit evaluation results for the four models

Longitudinal markers	Log likelihood	AIC	BIC
ADAS-Cog11	-6774.46	13584.92	13660.82
ADAS-Cog13	-7199.75	14435.50	14511.40
MMSE	-5513.41	11062.83	11138.73
FAQ	-6627.04	13290.09	13365.99

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 4
Comparison of prediction accuracy for the four longitudinal markers at different times (AUC)

Longitudinal markers	Δt (month)	9				18	
	t (month)	42	48	54	60	48	60
ADAS-Cog11		0.719	0.806	0.731	0.645	0.763	0.655
ADAS-Cog13		0.752	0.811	0.673	0.636	0.758	0.654
MMSE		0.760	0.689	0.753	0.665	0.697	0.687
FAQ		0.819	0.792	0.852	0.792	0.786	0.736

were also sensitive to the changes of AD and MCI populations over time (Harrison et al., 2018). Meta-analysis by Li et al. also showed that lower MMSE scores and higher ADAS-Cog scores resulted in a higher risk of cognitive decline from MCI to AD (Song et al., 2018). Some studies have suggested that the best performing combination of predictors in MCI and mild AD populations is the combination of the FAQ with ADAS-Cog13(Wessels et al., 2015). Tappen E, et al used Mini-Cog-FAQ and MMSE-FAQ in cognitive screening of older African Americans, Hispanic Americans, and European Americans (Tappen et al., 2010). Jutkowitz, et al used longitudinal data of MMSE-FAQ and the Neuropsychiatric Inventory Questionnaire (NPI-Q) to evaluate cognitive trajectories of 457 patients with mixed effects linear regression models (Jutkowitz et al., 2017). Therefore, when assessing dementia in older people and patients with MCI, we should consider combining cognitive measurements with social function assessment to predict the risk of AD. Due to the difference of cultural level and social background in different countries or regions, the diagnosis and treatment pattern have influence on the neuropsychological assessment results (Wu et al., 2020). The joint model can be used to select the appropriate screening tools based on local conditions and data.

Regular cognitive screening for MCI may help personalize care plans for patients and home caregivers. Medical staff can conduct regular follow-up assessment of cognitive function, social function, or other markers, and intervene in time to delay the progress of the disease. However, because the overall prevalence rate is low in the primary health care environment, it is still controversial to screen patients with cognitive impairment. Also, there is a misunderstanding that people believe AD is natural aging and the visit rate of dementia is low. Some patients only go to check when their disease develop to severe or when they can't even take care of themselves. If patients are examined with neuropsychological tests during community management, the participation of the elderly may increase (Xue et al., 2017; Xue et al., 2018). For regions where AD primary screening start late, especially in non-specialist settings, it is easier to train and carry out repeated longitudinal cognitive/functional assessments. It is feasible and meaningful to spend time on non-medical personnel training. Non-specialists may further add capacity in the workplace and reduce physician workload (Islam et al., 2020). After the doctor has diagnosed the patient with MCI, a trained professional investigator can conduct cognitive and functional measurements on him in the ward. The mutual assistance group can also be established to carry out health education and follow-up, so as to track the patient's health status related to AD. This has obvious advantages, such as short training requirements, easy management, and high accessibility.

Regarding the influencing factors related to longitudinal markers, a large number of epidemiological studies have shown that cognitive function and functional impairment in patients with MCI is related to factors such as age, sex, educational level, lifestyle, and disease history. The results of our study suggest that age, marital status, educational level, sex, and the ApoE ε4 allele were related to the cognitive decline in patients with MCI; marital status was related to social dysfunction. Among them, whether educational level protects against cognitive impairment is still controversial. Currently, some studies have shown that lower levels of education are related to faster declines in cognitive function (Alley et al., 2007). However, studies also suggest that people who have been educated for a long time show rapid cognitive decline once they show clinical symptoms (Meng and D'Arcy, 2012; Soto et al., 2008). In our study, it was found that a high level of education had a protective effect on cognitive function and was helpful for improving cognition. In normal life, if older people exercise, do housework, shop, read, and learn, it can delay the decline of cognitive and social functions.

The present study has two limitations. First, a single longitudinal marker was considered in this study and a continuous potential variable was introduced to represent the patient's potential disease severity (Wang et al., 2017) . The joint modeling was extended to the multivariate joint model with multiple longitudinal markers proposed by He et al. (He and Luo, 2016). Future studies relied on multiple serial measurements that can enhance the predictive power are likely to help reveal the best combination of predicted AD risk in MCI. Second, the ADNI queue is a convenient sample, not an epidemiological queue, which likely resulted in recruiting more impaired participants. Scientific epidemiological queues will be better for the joint modeling.

This study suggests that using the cognitive and function impairment assessment scales to monitor cognitive decay provides an inexpensive way to follow the prodromal MCI population and measure AD conversion rate. Thus, they can be useful in non-specialist settings for predicting AD progression.

Author statement

Yu designed the study. Wu wrote the draft of the paper. Wu, Zhang, He and Wang were responsible for data acquisition, data analysis and manuscript revision. Cui, Ge, Han, Luo and Liu provided study materials and guidance. All authors are grateful to the participating subjects for their support and cooperation in making this research possible.

Declaration of Competing Interests

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

Acknowledgments

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNl (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical lmaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; Cere Spir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; Eurolmmun;F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson &Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies;

Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal lmaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih. org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. We thank Adam Phillips, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript. This work was supported by the National Natural Science Foundation of China under Grant number 81673277, 81973154, 81903418.

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