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Risk classification for conversion from mild cognitive impairment to Alzheimer's disease in primary care

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ABSTRACT

There is a pressing need to identify individuals at high risk of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) based on available repeated cognitive measures in primary care. Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we applied a joint latent class mixed model (JLCM) to derive a 3-class solution: low risk (72.65%), medium risk (20.41%) and high risk (6.94%). In the low-risk group, individuals with lower daily activity and ApoEε4 carriers were at greater risk of conversion from MCI to AD. In the medium-risk group, being female, single, and an ApoEε4 carrier increased risk of conversion to AD. In the high-risk group, individuals with lower education level and single individuals were at greater risk of conversion to AD. Individual dynamic prediction for conversion from MCI to AD after 10 years was derived. Accurate identification of conversion from MCI to AD contributes to earlier close monitoring, appropriate management, and targeted interventions. Thereby, it can reduce avoidable hospitalizations for the high-risk MCI population. Moreover, it can avoid expensive follow-up tests that may provoke unnecessary anxiety for low-risk individuals and their families.

1. Introduction

In recent decades, there has been a significant increase in human life span and improvements in general healthcare, leading to a dramatic increase in the proportion of older adults in the population (Ferri et al., 2005). Dementia is a major age-related disease manifesting in progressive and insidious deterioration in cognition, function and behavior until death (Hill et al., 2017; Xue et al., 2017). Alzheimer's disease (AD), accounting for the largest proportion of senile dementia, has devastating effects on patients and their families, and it is associated with significant societal and financial burdens (Reitz and Mayeux, 2014). The initial presenting symptom of AD is cognitive complaints, frequently represented by a difficulty in remembering new information (Pereira et al., 2018). In advanced stages, brain regions responsible for cognitive abilities are irreversibly damaged and cerebral compensatory reserves are gradually exhausted (Beheshti et al., 2017). Patients lose self-care abilities, including dressing, eating, and personal care (Scheltens et al., 2016). Despite significant funding and huge efforts by the global scientific and medical community, there have been numerous failures in the development of effective medicines for the treatment and prevention of AD (Alzheimers and Dementia, 2018; Bachurin et al., 2018).

Prior to the gradual development of overt dementia, many individuals experience mild cognitive impairment (MCI), which is generally deemed to be an intermediate transitional state between normal aging and AD. Existing longitudinal studies report that older adults with MCI have a 10%−15% annual risk of converting to probable AD (Manly et al., 2008; Petersen et al., 2009). However, a significant

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; FAQ, Functional Activities Questionnaire; HR, hazard ratio; JLCM, joint latent class mixed model; MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination

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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.

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number tends to remain stable over-time and some may even return to a "healthy" state (Minhas et al., 2017; Spasov et al., 2018). Currently available screening instruments can effectively detect individuals with overt dementia. However, it is difficult to predict conversion from MCI to AD. The development of effective and personalized strategies to identify and slow the progression of AD would enable preservation of greater autonomy and function for individuals, and reduce health insurance costs. Therefore, reliably predicting conversion of MCI to AD is focus of current research (Pereira et al., 2018; Spasov et al., 2018).

Previous studies have identified a series of markers of conversion from MCI to AD that can quantify disease progression. These included neuropsychological assessment, neuroimaging and clinical markers. Advanced imaging techniques such as magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (PET) hold promise for detecting development of neuropathological changes. Nevertheless, highly expensive high-tech procedures are inaccessible to large portions of the population and only collected in tertiary or highly specialized medical centers (Davatzikos et al., 2009). Moreover, traumatic procedures (e.g., lumbar puncture) and cerebrospinal fluid biomarkers are associated with invasive risks and resistance, high cost, and time constraints (Jr et al., 1999; Mosconi et al., 2010). Therefore, some of these technologies are not appropriate to enable large-scale benefit, because their incorporation into routine preventive healthcare may be complicated by practical considerations (Levy et al., 2016). In particular, the conversion from MCI to AD remains difficult to accurately predict in primary care settings, due to the lack of access to sophisticated technologies and expertise (Luk et al., 2017).

Given the dynamics and multidimensionality of the aging process, factors influencing the risk of conversion from MCI to AD, including demography, socioeconomics, health behaviors, and psychological characteristics, vary widely among the elderly (Anderlucci and Viroli, 2015; ProustLima et al., 2015). Obtaining such details will not require collection of extra information from patients. For example, sex, age, marital status, educational level are routinely collected in primary care. Neuropsychological test batteries can be as sensitive as physical biomarkers in the detection of and screening for cognitive impairment and dementia (Chapman et al., 2011; Dickerson et al., 2007; Fleisher et al., 2007). Brief information from neuropsychological tests could identify and track subtle cognitive changes that occur in the prodromal phase of disease. Such information could assist medical service providers with limited resources to effectively screen many routinely identify functional impairments (Bondi et al., 2017). It is worth noting that several neuropsychological tests at different time points more accurately reflect actual cognitive abilities (Xue et al., 2017).

Accurate identification of individuals within the MCI population at high risk of future AD could contribute to earlier close monitoring, appropriate management, and targeted interventions for appropriate patients; thus reducing avoidable hospitalizations (Barnes et al., 2014; Lin et al., 2013). In contrast, low-risk individuals do not need expensive follow-up tests, which may provoke unnecessary anxiety for the patient and their families (Barnes et al., 2014). At present, risk models use different known risk factors to identify high-risk individuals in the MCI population (Stephan et al., 2010). However, no reported models are universally accepted with high predictive accuracy (Hou et al., 2018). Furthermore, there is little agreement that primary healthcare physicians can obtain better results for cognitive screening (Panayiotis et al., 2010). A predictive strategy for primary care should therefore be constructed using existing or readily available information (Hou et al., 2018).

In this study, we selected longitudinal behavioral markers (i.e., cognitive and daily activity ability), demographic risk factors (i.e., age, marital status, and educational level) and individual genetic risk factors (i.e., sex and APOE status) to construct a risk forecasting model. With this model, we classified the MCI population into different risk categories, and implemented individual dynamic prediction in primary care.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu) from 2005–2014. The primary goal of ADNI has been to test whether serial MRI, PET, biological markers, and clinical and neuropsychological assessments can be combined to measure progression of MCI and early AD (Weiner et al., 2012). For the ADNI study, written informed consent was obtained for all participants and the study protocol was approved by the institutional review board at each participating center, before protocol-specific procedures were performed. General guidelines for the diagnosis of MCI incorporate the presence of objective cognitive deficits with Mini Mental State Examination (MMSE) scores (between 24 and 30, inclusive) (Gerstenecker and Mast, 2014), global Clinical Dementia Rating (CDR) scores (0.5), and the preservation of activities of daily living (ADLs) (Petersen et al., 2009). As such, the condition does not qualify as a diagnosis of dementia. For the ADNI database, diagnosis of AD was based on the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria. For more up-to-date information see www.adni-info.org.

Participants were included in the current study if they were over 65 with a diagnosis of MCI at baseline, including those who developed AD during the follow-up period of ADNI 1, ADNI 2, or ADNI GO. Participants with MCI were carefully selected to include those with documented memory disorders, and to exclude those with damage that may have other potential causes. Neuropsychology data with an average follow-up of 6 months was extracted for 245 eligible participants. Participants with MCI converting to AD were included, not other forms of dementia. Neuropsychology data after participants developed AD were not included in the analysis. Participants had been administered a multi-test cognitive battery every 6 months, with a brief cognitive screening instrument (the MMSE) and a functional scale, the Functional Activities Questionnaire (FAQ). Furthermore, demographic data and APOEε4 status (present or not) were obtained from the baseline visit.

2.2. Statistical analysis

Except for age at study entry and MMSE scores, which were continuous scores, other covariates in the model were re-coded as binary variables to enable estimation of class-specific parameters. These included sex (male/female), educational level (medium, 12 years/high, more than 12 years), ApoEε4 status (present/absent), FAQ score (≤ 9/>9), survival outcome (MCI/AD), and marital status (single: unmarried, divorced, separated, or widowed/married). Basic model specifications are detailed below. Continuous variables are shown as mean (standard deviation (SD)).

Given the heterogeneity of the elderly population, we used a joint latent class mixed model (JLCM) to simultaneously model longitudinal biomarkers and events (Lin et al., 2002). The JLCM linking longitudinal quantitative outcomes with time-to-event data by several statistically defined homogeneous subgroups were found to flexibly capture correlations, offering a better framework to handle additional heterogeneity and identifying distinct sub-populations (Rouanet et al., 2016). When the classification increased, baseline risk of the event could be changed flexibly with the marker trajectory.

The JLCM was developed with three ingredients: class membership, longitudinal marker trajectories, and hazard for the time-to-event process (Proust-Lima et al., 2014). Supposing that the population is heterogeneous, N participants from a random sample ($N = 245$ in our ADNI sample) could be divided into G finite unobserved subgroups (i.e., latent classes), which were characterized by distinct cognitive evolution profiles and risk functions for the event of interest. Latent classes

linking cognitive factors and the onset of AD could be derived with a multinomial logistic regression model. The longitudinal sub-model captured complex trajectories of cognition over time according to sex, education level, marital status, ApoEε4, and FAQ score within a linear mixed effect model. The survival sub-model, developed with a proportional hazard model, may fit the survival process using the same covariates as those used for the longitudinal sub-model.

Parameter estimations for the JLCM were performed in the maximum likelihood framework for a given number of latent classes, G (Titterington et al., 1985). The optimal number of latent classes was identified with the minimum principle of the Bayesian Information Criterion (BIC) (Schwarz, 1978). A previously developed test score could be used to check the conditional independence assumption (Jacqmin-Gadda et al., 2010). Individual posterior probabilities pertaining to each latent class could be gained given all the information. The discrimination of the model depended largely on the results of posterior classification and the identifiability of latent classes. The proportion of participants with their maximal posterior latent class membership probability was in general above 0.8 or 0.9 (Molenberghs and Kenward, 2008). The posterior classification table provided the mean posterior probabilities for participants classified into each class. For the latter, an ideal discriminatory classification would have diagonal terms close to 1 and non-diagonal terms close to 0.

In the framework for the JLCM, subject-specific prediction could be implemented. Either individual prediction values over all classes or class-specific prediction value over all individuals could be obtained. Individual dynamic cumulative incidences of latent classes were derived given covariates, repeated cognitive measures, and conversion from MCI to AD within a window of time [s, $s + t$] up to the time of prediction, s. Descriptive statistical analysis was performed with SPSS 22.0 and the JLCM was implemented in the Jointlcmm function of R (http://cran.r-project.org/web/packages/lcmm). P values of less than 0.05 were considered significant.

3. Results

Table 1 presents background characteristics of the 245 participants. At the end of follow-up, a minority of individuals (N = 71, 29.0%) were reported to have undergone conversion to AD, with the majority remaining in the MCI state.

Table 2 displays four candidate models. The BIC value changed little between models 2 and 3. To facilitate interpretation of the model and multiple categories for the population, the 3-class solution was preferred to ensure that dependency between times-to-AD and longitudinal cognitive trajectory was captured, and the conditional independence assumption was not rejected (P = 0.37). The three estimated class membership probabilities were π_1 = 72.65%, π_2 = 20.41%, and π_3 = 6.94%.

Table 1
Summary characteristics of 245 MCI individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) during 2005–2014, where continuous variables are summarized as mean (standard deviation (SD)), categorical variables are summarized as counts and frequencies (%).

Characteristics	Mean (SD) or n(%)
Age (year)	74.0 (5.5)
Gender	
Male	145 (59.2%)
Female	100 (40.8%)
Marital status	
Married	178 (72.7%)
Single	67 (27.3%)
Education	
Medium education	45 (18.4%)
High education	200 (81.6%)
ApoEε4	
Present	109 (44.5%)
Absent	136 (55.5%)
MMSE score	27.9 (1.73)
FAQ score	2.6 (3.5)

Abbreviations: FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination; SD, standard deviation.

3.1. The 3-class solution

An average of 72.65% individuals were allocated to class 1, which represented the lowest risk rates (close to zero) for dementia before the age of 78, as well as the smallest mean decline in MMSE score with age. It is worth noting that the risk of conversion from MCI to AD after 78 years increased. Class 1 was designated the “low-risk group”.

Class 2, the “medium-risk group”, was associated with an increased risk of MCI conversion to AD after 65 years old. Individuals allocated to this group began with cognitive levels similar to those in class 1, which remained stable until around 66 years of age where a gradual progressive cognitive decline began.

Class 3 comprised the minority of the population (6.94%) and was designated the “high-risk group” because it was associated with the highest risk of conversion from MCI to AD, with a sharper downward trend in MMSE scores than in classes 1 and 2. Overall, cognitive levels in class 3 were poor throughout the trial period. Estimated mean MMSE score evolution and survival functions associated with conversion from MCI to AD in the three classes are illustrated in Figs. 1 and 2, respectively.

3.2. Goodness of fit of the model

Given maximum posteriori attribution probability of the three classes, we quantified the discriminatory ability of the model. The probability of belonging to the allocated class was above 90%, with probabilities of 96.25%, 92.58%, and 99.96% in classes 1 to 3, respectively. The mean probability of belonging to another class was less than 6.8%. A posteriori classification table providing mean values of posteriori probabilities for individuals in each class supported a robust fit of the model to the data (Table 3). Variation curves of the observed and predicted values over time are presented in Fig. 3. These show that the model fitted well to each class.

3.3. Covariate influences on conversion from MCI to AD

In the longitudinal sub-model, the impact of FAQ scores on cognition was statistically significant for the entire elderly population. In the low-risk group, the regression coefficient for the FAQ was −0.90 (95% confidence interval [CI] = −1.36, −0.44; P <0.001), suggesting that cognition decreased significantly with increased FAQ over time. Analogously, the coefficients for other factors such as education level (−0.52; 95%CI = −1.01, −0.02; P = 0.04) and ApoEε4 status (−0.68; 95%CI = −0.98, −0.37; P <0.001), suggested that individuals with lower education levels and ApoEε4 carriers had a tendency to greater cognition decline. In the medium-risk group, ApoEε4 carriers (β = −1.50; 95%CI = −2.06, −0.93; P <0.001) and those with lower daily activity ability (β = −2.24; 95%CI = −2.74, −1.75; P <0.001) had a greater degree of cognitive impairment. In the high-risk group, lower daily activity ability (β = −6.16; 95%CI = −6.88, −5.44; P <0.001) had greater cognitive decline. Furthermore, single individuals had poorer cognition than did married individuals (β = −2.61; 95%CI = −4.25, −0.98; P = 0.002).

In the survival sub-model, different factors affected different groups. In the low-risk group, compared with individuals without ApoEε4, ApoEε4 carriers had 2.60 times the risk of conversion from MCI to AD (95%CI = 1.31, 5.15; P = 0.006). Lower daily activity ability may also increase the risk of conversion from MCI to AD (hazard ratio [HR] = 3.15; 95%CI = 1.03, 9.66; P = 0.05). In the medium-risk

Table 2
Summary of 4 candidate models derived from the Joint Latent Class Mixed Model (JLCM): number of latent classes(G), Log-likelihood, number of parameters, Bayesian Information Criterion (BIC) and latent class proportion (in%).

Candidate model	G	Maximized Log $L^{(G)}$	No. of parameters	BIC	Class1 (%)	Class2 (%)	Class3 (%)	Class4 (%)
Model1	1	−4967.954	22	10,056.936	100.00			
Model2	2	−4735.473	44	9713.001	8.16	91.84		
Model3	3	−4684.528	66	9732.138	72.65	20.41	6.94	
Model4	4	−4464.628	88	9813.367	6.94	75.51	11.02	6.53

Abbreviations: BIC, Bayesian Information Criterion.

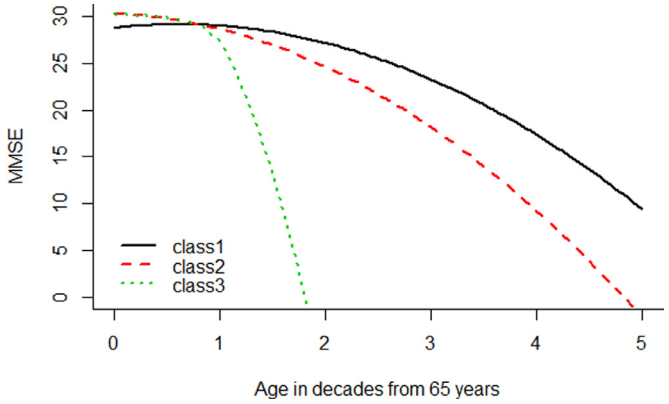

Fig. 1. Predicted class-specific cognitive trajectories over time from the 3-class joint latent class mixed model (JLCM), Among 245 mild cognitive impairment (MCI) individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) during 2005–2014.

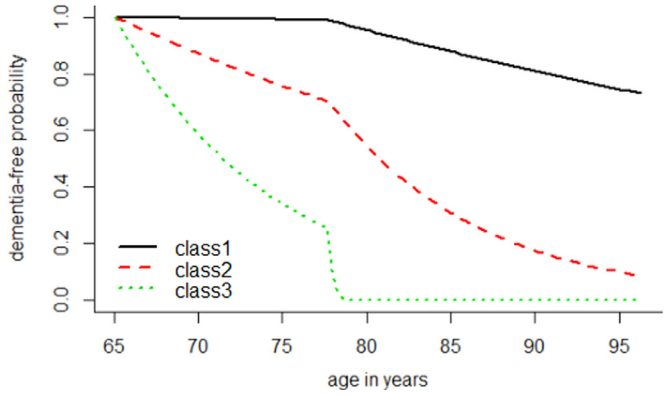

Fig. 2. Predicted class-specific risk rates for dementia over time from the 3-class joint latent class mixed model (JLCM), Among 245 mild cognitive impairment (MCI) individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) during 2005–2014.

Table 3
A posteriori classification table from the 3-class Joint Latent Class Mixed Model (JLCM), providing the mean value of posteriori probabilities for individuals in each class.

	Prob1	Prob2	Prob3
Class1	0.9625	0.0307	0.0068
Class2	0.0675	0.9258	0.0067
Class3	0.0001	0.0003	0.9996

group, lower daily activity ability (HR = 4.36; 95%CI = 1.76, 10.80; $P = 0.001$) and being single (HR = 6.59; 95%CI = 1.92, 22.60; $P = 0.002$) increased the risk of conversion from MCI to AD. The risk of conversion from MCI to AD in women was 2.66 times that of men (95%CI = 1.30, 5.45; $P = 0.007$). The risk of conversion from MCI to

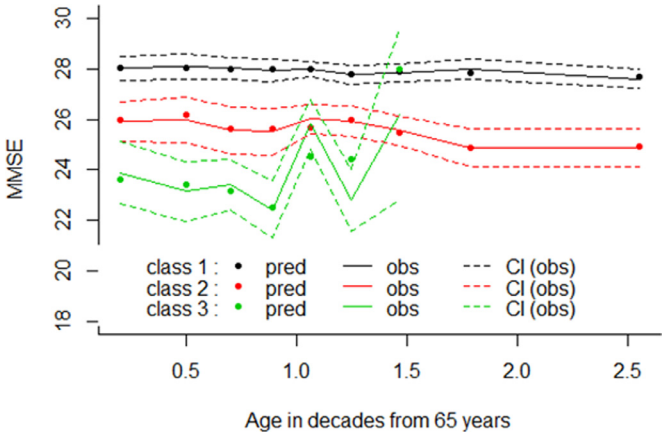

Fig. 3. Weighted observations and weighted mean of subject-specific predictions from the 3-Classjoint latent class mixed model (JLCM), Among 245 mild cognitive impairment (MCI) individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) during 2005–2014.

AD in ApoEε4 carriers was 2.22 times that of individuals without ApoEε4 (95%CI = 1.25, 3.97; $P = 0.007$). In the high-risk group, there was higher risk of conversion from MCI to AD for individuals with a lower education level than those with a higher education level (HR = 2.76; 95%CI = 1.08, 7.02; $P = 0.03$). Moreover, single individuals at high risk had an greater risk of conversion from MCI to AD compared with married individuals (HR = 16.57; 95%CI = 2.08, 131.82; $P = 0.008$). Table 4 presents parameter estimations of the survival and longitudinal sub-models.

3.4. Individual dynamic prediction

To exemplify the individual dynamic cumulative incidence calculated from the JLCM, we predicted the incidence of conversion from MCI to AD after 10 years for a married man of 75 years old who did not carry ApoEε4, who entered the cohort at 66 years old, was highly educated, and had high daily activity. Fig. 4 shows the incidence of conversion from MCI to AD was essentially 0 at the age of 71, and then gradually increased. The man had a probability of experiencing AD of 20% up to 85 years old.

4. Discussion

4.1. Characterization of covariate influences

Making full use of quantitative cognitive scores, the population with MCI was divided into three groups: low-risk, medium-risk group, and high-risk. For each of these, traditional covariates had differing effects on the conversion from MCI to AD.

Our results indicate that gender plays an important role in the conversion from MCI to AD. Among people over 65 years of age, the probability of having AD was 2 to 3 times higher for women than for men of the same age (Chandra et al., 2001). Hippocampal atrophy and neurofibrillary tangles develop more quickly in women with such that

Table 4
Parameter estimates and 95% confidence intervals (CI) of the 3-class longitudinal sub-model and survival sub-model, among 245 Mild Cognitive Impairment (MCI) individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) during 2005–2014.

Variable	Class1			Class2			Class3		
	Coefficient	95% CI	P	Coefficient	95% CI	P	Coefficient	95% CI	P
Longitudinal sub-model									
Intercept	29.91	28.74,31.08	<0.001	31.56	29.00, 34.12	<0.001	27.57	24.60,30.54	<0.001
Gender	0.05	−0.34, 0.45	0.79	−0.82	−2.12, 0.48	0.22	1.58	0.32, 2.84	0.01
Educational level	−0.52	−1.01, −0.02	0.04	0.03	−1.00, 1.07	0.95	−1.20	−2.57, 0.18	0.09
Marital status	0.02	−0.40, 0.45	0.92	−0.96	−2.70, 0.78	0.28	−2.61	−4.25, −0.98	0.002
ApoEε4	−0.68	−0.98, −0.37	<0.001	−1.50	−2.06, −0.93	<0.001	−0.19	−0.98, 0.61	0.65
FAQ	−0.90	−1.36, −0.44	<0.001	−2.24	−2.74, −1.75	<0.001	−6.16	−6.88, −5.44	<0.001
Survival sub-model[†]									
Intercept	1.03	0.98,1.07	0.23	1.18	0.96,1.46	0.13	1.39	0.78,2.47	0.26
Gender	0.90	0.31, 2.57	0.84	2.66	1.30, 5.45	0.007	1.92	0.75, 4.93	0.18
Educational level	0.76	0.26, 2.24	0.62	0.51	0.18, 1.46	0.21	2.76	1.08, 7.02	0.03
Marital status	0.89	0.36, 2.17	0.79	6.59	1.92, 22.60	0.002	16.57	2.08, 131.82	0.008
ApoEε4	2.60	1.31, 5.15	0.006	2.22	1.25, 3.97	0.007	1.48	0.77, 2.81	0.24
FAQ	3.15	1.03, 9.66	0.05	4.36	1.76, 10.80	0.001	2.57	0.80, 8.22	0.11

Abbreviations: CI, confidence interval; FAQ, Functional Activities Questionnaire.
[†] For the Survival sub-model, the coefficient is hazard ratio.

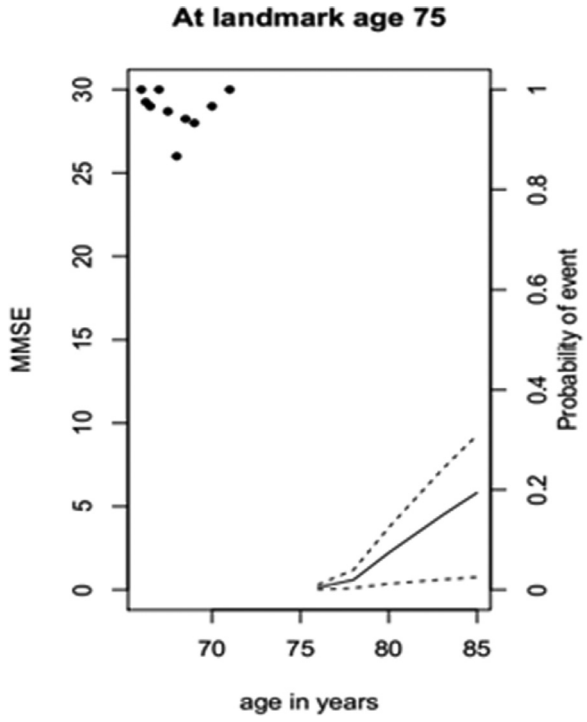

Fig. 4. Individual dynamic prediction of dementia at landmark ages 75 years old. The male, middle school and above, married, did not carry ApoEε4, Functional Activities Questionnaire (FAQ) = 2.01,"●"denoted his cognition from 66 years old to 71;"—"denoted the incidence of dementia;"—"denoted confidence interval of the incidence of dementia.

they show a more rapid loss of autonomy and cognitive decline compared with men (Barnes et al., 2005). The organizational and activational role of estrogen in this has been confirmed by previous research (McEwen and Milner, 2017; Pinares-Garcia et al., 2018). However, there has been some degree of controversy. For instance, there is no obvious gender difference in the risk of developing AD, as highlighted increasing numbers of epidemiologists. This may be because of misclassification of AD, which occurs at different rates for men and women or may be due to the fact that women live longer (Mielke et al., 2018). Results of the current study indicate that in the medium-risk group, the risk of conversion from MCI to AD was significantly higher among women than among men. As such, the effect of gender on development of AD needs further study.

According to a review of the literature, there is no consensus about the mechanism by which educational level exerts effects on cognition function. For example, cognitive reserve theory suggests that during the process of education, individuals may increase reserves through the addition of dendritic branches and other mechanisms to improve cognitive function (Bickel and Kurz, 2009; Hugo and Ganguli, 2014; Meng and D'Arcy, 2012; O'Shea et al., 2015). In contrast, brain reserve theory proposes that the faster the rate of cognitive impairment, the higher the risk of AD, with longer periods of education (Wattmo et al., 2011). Our study is consistent with the cognitive reserve hypothesis as they indicate that higher education levels are associated with lower risk of conversion from MCI to AD, as well as less cognitive impairment. Nonetheless, the relationship between educational level and the conversion from MCI to AD requires further investigation.

Generally speaking, marriage appears to contribute to maintenance of a favorable cognitive state. This may partly be due to the fact that married individuals undertake more communicative activities, which stimulates neurons and protects from cognitive degeneration (Lipnicki et al., 2013; Yaakov, 2012). In particular, the mental health of married elderly individuals is often better than that of widowed or single people (Kuiper et al., 2015; Sommerlad et al., 2017; Wang et al., 2019). The spouse plays an important role in quality of life for the elderly, as they may not only provide care for their partner, but also spiritual comfort (Sander and Ruth, 2016). Our study results agree with previous research to show that singleness is associated with a greater risk of cognitive decline. It is worth mentioning at this point that ADNI requires participants to have a learning partner. Married elderly people tend to have a readily available learning partner (their spouse) while single people do not necessarily, as they are often single following the death of their spouse. Therefore, selection bias and confounding cannot be ignored in this sample. However, it appears that staying married (where possible) is beneficial for elderly people, and they should seek support from and interactions with spouses, friends, and family members to reduce the risk of cognitive impairment.

APOEε4 is a well-established biogenetic risk factor for late-onset AD (Aggarwal et al., 2005; Hendrie et al., 2014; Hsiung et al., 2004). APOEε4 affects the primary seeding stage of amyloidal formation by increasing amyloidal deposition and accumulation of hyperphosphorylated tau at later stages, thus leading to neurotrophy (Liu et al., 2017). Genetic studies conducted with ADNI data have confirmed that APOEε4 is associated with hippocampal atrophy and cognitive dysfunction (particularly memory), thereby increasing disease risk and lowering age of onset (MR et al., 2004). The presence of a single ε4 allele increases the risk of conversion from MCI to AD by 2–3 times, while 2–4 alleles increased the risk by nearly 11 times (Hsiung et al.,

2004). In the current study, we observed that ApoEε4 carriers not only had an increased risk of conversion from MCI to AD, but also had a greater decline in cognitive function in the low-risk group and medium-risk group. The genetic risk did not reach significance possibly due to the omitted predictors, attenuated power, or unknown confounding variables (Risacher et al., 2015; Qian et al., 2017). Undoubtedly, further research and validation into the impact of the genetic risk may advance our prediction of AD course. Taken together, active preventive treatment should be conducted in the early stages for ApoEε4 carriers with MCI to reduce the risk of conversion to AD and reduce impairments in cognitive function.

Following earlier similar work, we observed that more informant-reported functional deficits are associated with a 4-fold increase in conversion from MCI to AD during long-term follow up (Tabert et al., 2002). These empirical findings support the hypothesis that daily activity abilities show subtle but significant deficits despite the fact that MCI criteria excluding substantial functional deficits (Xue et al., 2012). The FAQ is an essential instrument to identify any signs for alarm because minor disruption of daily function can indicate the latter phases of disease progression in individuals with MCI (Brown et al., 2011). It is possible that higher daily activity ability and rich social engagement stimulates blood circulation in the striatal circuit of the prefrontal cortex, such that maintaining a pleasant mood improves cognitive function (Gill et al., 2011). The FAQ is particularly promising from the perspective of public health due to its modifiable nature. Nonetheless, it is rather remarkable that an established and universally accepted quantitative metric threshold of functional decline to precisely separate MCI from AD has not been determined. To remedy this, potential biological mechanisms underlying disruption of instrumental daily activities should urgently be identified.

4.2. Cognitive screening in primary health care

Various case identification strategies for dementia have been proposed. Relying on baseline and cognitive data to predict the risk of conversion from MCI to AD has limited accuracy, ranging from 65%−84% (Gomar et al., 2011; Michael et al., 2012; Walters et al., 2016). In our previous studies, we used the growth mixed model (GMM) to classify the risk of MCI based on ADNI data and the average posterior probabilities of three groups obtained were 87.12%, 81.61% and 92.79%, respectively (Zhi-Xin et al., 2018). Using the GMM model for ADNI data in this paper, we also derived three different risk groups. Membership probabilities and average posterior probability of three estimated class were 81.86% vs 82.44% for low-risk group, 16.29% vs 84.99% for medium-risk group, and 1.86% vs 91.67% for high-risk group, respectively. In contrast, we used the JLCM model to predict conversion from MCI to AD with over 90% accuracy. Moreover, it is worth noting that JLCM model can provide individual dynamic predictions while the GMM model is only capable of performing risk classification. In summary, it could be thought that JLCM was superior to GMM in screening high-risk groups. Because the overall prevalence rate is low in primary healthcare, how best to identify patients with cognitive impairment remains a controversial topic. Regular cognitive screening for MCI in primary healthcare settings may contribute to developing individualized care plans for patients and family caregivers (Thyrian et al., 2012). Due to the limited availability of specialists (e.g., psychiatrists) and the under-documentation of cognitive impairment, assessment and management of cognitive impairment will mainly fall on primary care practitioners (Panayiotis et al., 2010). Increasing attention should therefore be paid to the training of primary healthcare physicians in cognitive screening (Flaherty et al., 2018).

Admittedly, the shortcomings of the MMSE, including its dependence on population variables such as age and education, cannot be ignored (Larner, 2018). MMSE is not specifically designed for primary care. However, it does have obvious advantages, such as short training requirements, ease of administration, and high accessibility (Cannon and Larner, 2016; Tong et al., 2016). In fact, an effective assessment tool that can be used without the presence of physicians may be even more preferable (Rosenbloom et al., 2018). Further research is required to develop an appropriate and effective cognitive assessment tool for primary care.

4.3. Limitation

The current study is subject to several limitations that ought to be acknowledged. First, the ADNI cohort was a convenience sample rather than an epidemiological cohort, which likely resulted in recruitment of more cognitively impaired subjects who were taking several medications for AD, MCI, or other conditions that may affect the results. Second, variability in MCI is not fully considered, such as amnestic and non-amnestic groups. Further effort is required to validate biomarkers criteria, in order to make them suitable for application at primary care.

Despite these limitations, the method used in this study enabled a medical service provider to identify high-risk individuals and provides a powerful argument in favor of the joint model for handling heterogeneous longitudinal data. The key strength of this work is the statistical method, which is likely to have clinical and economic utility.

Conflict of interest declaration

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

Description of authors' roles

In this work, the contribution of each author is essential. Author Hongmei Yu raised new questions and ideas about this article. Author Ruifeng Liang and Xiaoyan Ge provided conceptual guidance on Alzheimer's disease, cognitive impairment, etc. Author Long Liu, Liye Zhou were responsible for data acquisition and download. Data were obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The investigators within the ADNI contributed to the design and implementation of ADNI. Author Tong Wang prepared and confirmed statistical methods. Author Haihong Xue and Hongjuan Han conducted data analysis. Author Yao Qin was responsible for interpretation of results and writing of the article. Author Hongmei Yu and Yuling Tian conducted the literature review and made critical revision. All authors promise to take public responsibility for appropriate portions of its content.

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