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A semiparametric method for estimating the progression of cognitive decline in dementia

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ABSTRACT

Although many patients develop cognitive decline, their trajectories of cognitive decline are diverse and incompletely understood. Accurate prediction of the cognitive decline process is critical for early treatment and management of dementia. We used the Clinical Dementia Rating Score Sum of Boxes (CDR SUM) score as a cognitive decline proxy, and investigated factors that are potentially associated with cognitive decline, including duration, age at onset, sex, education, health-related symptoms, and neuropsychiatric symptoms. We analyzed data from an established 10-year longitudinal patient registry of patients diagnosed with non-normal cognition. We compared a multi-level polynomial regression model and two semiparametric mixed-effects models, and applied Nakagawa and Schielzeth's R^2_{GLMM} and correlation coefficient as model selection criteria. The semiparametric method was selected to describe and predict the cognitive decline trajectory. Neuropsychiatric symptoms were indicators of a higher CDR SUM score. History of stroke, presence of disinhibition, and nighttime behavior disturbances were also associated with higher CDR SUM score. Older age of onset ($>$ 86 years), educational level higher than high school education ($\geq$ 12 education years), and the presence of irritation were indicators of slower cognitive decline. The semiparametric model can assist in estimating cognitive decline in terms of CDR SUM score, given individual characteristics.

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Cognitive decline; dementia; modeling; multi-level; semiparametric

1. Introduction

Dementia is a devastating disease and highly prevalent in older adults. People with dementia experience loss of cognitive function to the extent that it interferes with their social and/or occupational functions. Symptoms include a loss of the ability to think, remember, and reason. Late symptoms may include the loss of muscle and reflex function, which can lead to difficulties in swallowing and coughing (National Institutes of Health, 2013). Alzheimer's is the sixth-leading cause of death in the United States and the fifth-leading cause of death for individuals age 65 and older (Alzheimer's Association, 2013).

Alzheimer's disease (AD) is the most common type of dementia, accounting for 60% to 80% of dementia cases. It is reported that about 11% of people aged 65 years and older have AD, and the highest risk is among those aged 85 years and older (32%) (Alzheimer's Association, 2015). Considering its high prevalence and devastating effect, it is critical to understand the progressive course of dementia.

The rate of progression of dementia is highly variable; investigating patterns of its progression is, therefore, a valuable research avenue. Mild cognitive impairment (MCI) is often regarded as an intermediate state on a one-way path from normal cognition to dementia (Morris *et al.*, 2001). Patients with MCI experience mild but measurable changes in thinking abilities; these changes are noticeable to the person affected and to family members and friends, but do not affect an individual's ability to carry out everyday activities (Alzheimer's Association, 2016). MCI includes heterogeneous types of cognitive dysfunction that manifest as symptoms of cognitive decline. Furthermore, in a review of population-based studies, adjusting for sample size, Mitchell and Shiri Feshki (2009) found that the cumulative proportions of patients with Mayo-defined MCI who progressed to AD, to vascular dementia, and to other forms of dementia were 28.9%, 5.2%, and 21.9%, respectively. Therefore, not all patients with MCI deteriorate over time.

Due to the heterogeneity of patients with MCI, the pattern of cognitive decline is still largely unpredictable to patients and their families; it is essential to predict how severe cognitive and functional disability will be over time, or for how long patients can be expected to survive. This knowledge would help patients and families to plan for management of the disease, as well as future financial and other care arrangements. Knowledge about the progression of cognitive decline would also facilitate the planning of clinical trials for proposed treatments. Furthermore, it would help establish eligibility criteria for services where functional ability assessment is needed to receive reimbursements, thus providing a reference for governments or insurance agencies to estimate medical costs.

In past studies, the following factors have been reported as those that most commonly indicate a fast progression of cognitive decline: female sex (Tschanz *et al.*, 2011; Peters *et al.*, 2015); fewer years of education (Shadlen *et al.*, 2005); early-onset cognitive impairment (before the age of 65 years) (Lindsay

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et al., 2002); vascular health conditions (Baumgart *et al.*, 2015); and the presence of psychosis symptoms (Lyketsos *et al.*, 2002; Mortimer *et al.*, 1992). The subjects of these studies are mostly community dwelling, and sufficiently strong evidence has been established that those factors influence dementia progression rate.

Several quantitative studies have investigated patterns of dementia progression. Chaves *et al.* (2010) performed a Cox regression analysis for survival and found that vascular risk factors and less education are strong predictors of a fast decline. A mixed survival model was used by Yu and Ghosh (2010) to jointly estimate dementia onset and death. They reported that the acceleration of cognitive decline in subjects with higher education levels occurs later, but at a faster rate than that in subjects with lower education. Chaves *et al.* (2010) and Yu and Ghosh (2010) placed greater emphasis on survival and time point estimation of dementia onset. Wilkosz *et al.* (2009) found that 201 patients with AD showed six trajectories with significantly different courses and rates of cognitive decline. In their study, the initial Mini-Mental State Examination (MMSE) score and age were the concomitant variables included in their latent class trajectory model. They found that more severe psychotic symptoms increased the probability of a more rapid cognitive decline, and that APOE $\varepsilon 4$ was not associated with any of these distinct trajectories. Although the findings are quite informative, the latent class trajectories were from a relatively small sample. The study did not make predictions about future cognitive decline. None of these studies formulated a prediction model to explain the influence of risk factors in a trajectory pattern for cognitive decline.

In order to mitigate the research gap of the personalized trajectory estimation model, our study aims to establish a robust, specific, and accurate quantitative prediction model with low cost and high efficiency. The trajectory prediction model for cognitive decline would not only explain the known cognitive decline course but also make an effective prediction about future trends of cognitive decline based on individual medical profiles. The prediction models were developed from a 10-year longitudinal patient registry of patients diagnosed with non-normal cognition. The selected model is ready to use and can be implemented in non-clinical settings without needing to acquire biomedical specimens or radiological results. It would be a practical tool for medical providers, caregivers, and other interested parties to predict the cognition deterioration course for patients with cognitive decline onset. We used the Clinical Dementia Rating Score Sum of Boxes (CDR SUM) score as an overall indicator of cognitive and functional levels and explored the typical trajectory of those who had prevalent cognitive decline. The Washington University CDR is a global assessment instrument that is regularly used in clinical and research settings to assess dementia severity (O'Bryant *et al.*, 2008). On the CDR, cognitive functioning is rated in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR evaluation is administered by a clinician or trained health professional using a structured form that is based on informants' (close friends, families, or caregivers of the patient) reports, as well as behavioral and neurological examinations of the patient. A CDR-0 denotes normal cognition, and CDR-3 represents the most severe stage of dementia. The CDR SUM score is the sum of each of the domain box scores, with scores ranging from 0 to 18. O'Bryant *et al.* (2008) studied dementia using categories based on the range of CDR SUM scores, and classified CDR SUM scores of 0.5–4.0 as questionable cognitive impairment, 4.5–9.0 as mild dementia, 9.5–15.5 as moderate dementia, and 16.0–18.0 as severe dementia. The CDR SUM score gives practical information on how well a patient can function independently, and provides a better understanding of cognitive well-being. Moreover, its precision allows changes over time to be tracked (Howieson *et al.*, 2008).

For longitudinal studies, multilevel (ML) models were widely used in disease progression modelling, including periodontal disease (Gilthorpe *et al.*, 2003), chronic kidney disease (Eriksen *et al.*, 2006), multiple sclerosis (Lawton *et al.*, 2015), and HIV/AIDS (Seid *et al.*, 2015). A semiparametric mixed-effect (SME) model was used to capture the trajectory of lung function decline in cystic fibrosis (Szczesniak *et al.*, 2013). As a pioneer study that establishes a sound prediction model to quantify cognitive decline trajectory, we compared the two modeling applications on estimating CDR SUM score for patients with cognitive decline. We jointly used correlation coefficient and Nakagawa and Schielzeth's R-square to evaluate the goodness-of-fit of models. The prediction model may help families and healthcare providers to better understand cognitive decline trajectory and make a management plan; furthermore, it can help to quantify and discern treatment effects in future medical trials for dementia.

The rest of the article is organized as follows. Section 2 presents the data for developing models and explains the two modeling methods. Section 3 details the model application, model evaluation, model validation with test data, and analyzed prediction outcomes. Section 4 summarizes the findings in the context of the literature and discusses the limitations and future work.

2. Methods

Mixed-effects models are very powerful tools for modeling longitudinal data, which involve repetitive measurements on the same subject over a period of time. These data may also contain many covariates and complex relationships. To map the pattern underlying these variables, a multilevel (ML) model and a semiparametric mixed-effects (SME) model were used to fit subject-specific curves. In the following, we first describe the data used, followed by a discussion of the ML and SME models.

2.1. Data

The data were publicly available and provided by the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) database. The NACC database is one of the largest and most comprehensive databases of its type in the world. The data are contributed by 39 past and present Alzheimer's Disease Centers supported by the U.S. National Institute on Aging. NACC UDS is a cumulative database including demographic information, clinical evaluations, and neuropathology data from 2005 to the present. A description of the dataset can be found in Morris *et al.* (2006) and Weintraub *et al.* (2009). It is not a

population-based database. The subjects were referred by clinicians, self-referred by patients or family members, or actively recruited through community organizations. Only those who were diagnosed as having non-normal cognition were included in this study. All of the patients visited the center or made contact with the center annually until they died or withdrew.

We first prepared a training data set from patient data for the period September 1, 2005, through September 1, 2015, to investigate the relationships between variables, and then used test data for model validation. The training data set was obtained from Caucasian patients who were deceased by the time of data acquisition for model building, so that complete profiles of each patient from the first visit to death were included. Patients who had made only one visit were excluded. Assuming missing data arising at random, those who had missing or unknown values in any of the predictive variables were excluded. A total of 2669 patients and 9615 records were included in the training data set after application of these exclusion criteria.

In the test data, we included Caucasian patients who were surviving at the cut-off date of December 1, 2015 (beginning in September 1, 2005) from the NACC UDS database. After data cleaning of unknown or missing values in any predictive variables, the final test data consisted of 16 783 observations of 2996 patients. There were no overlapping in test data and training data because of the different period and different survival status. The overall population was highly variable in levels of cognitive decline (Fig. 1). As also seen in the current cohort, a number of longitudinal cohort studies have shown that patients with dementia do not display linear cognitive decline (Howieson *et al.* 2008; Doody *et al.* 2010; Cloutier *et al.* 2015), which indicates that a traditional linear regression model would not be sufficient in simulating the trajectory of cognitive decline.

2.2. Multilevel model

The ML model (also known as the hierarchical linear model or a nested data model) recognizes that data has hierarchical structures that allow each level to have residual components. Before modeling a relationship between a response variable and covariates, the data structure must be understood. The structure of data can be viewed as levels of grouped effects that lead to final observation results. The ML model uses the regression method and allows variables to have multiple levels with a zero-mean variance. In the present study, time was regarded as a first-level effect, and other time-related effects (including time-constant and time-varying effects) were regarded as second-level effects.

This approach assumes that CDR SUM scores are explained by the time since the onset of cognitive decline and a normally distributed residual. Likewise, the effect of time is explained by a superordinate effect (time-constant and time-varying covariates) and a normally distributed residual. A linearity assumption is not sufficient to capture the change in the trajectory curves, as shown in Fig. 1. We tested polynomial models with quadratic and cubic terms, but found that the slope of the cubic term was zero and could be discarded. Therefore, a quadratic curve was selected for the model. The model can be expressed as:

Level 0

$$y_{ij} = \beta_{0ij} + \beta_{1ij}t_{ij} + \beta_{2ij}t_{ij}^2 + \epsilon_{ij} \tag{1}$$

Level 1

$$\beta_{0ij} = a_{0ij} + U_{0ij} \tag{2}$$

$$\beta_{1ij} = a_{1ij} + U_{1ij} \tag{3}$$

$$\beta_{2ij} = a_{2ij} + U_{2ij} \tag{4}$$

$$\text{with} \quad \begin{pmatrix} U_{0ij} \\ U_{1ij} \\ U_{2ij} \end{pmatrix} \sim N \begin{pmatrix} 0 & \varphi_{00}^2 & 0 & 0 \\ 0, & 0 & \varphi_{10}^2 & 0 \\ 0 & 0 & 0 & \varphi_{20}^2 \end{pmatrix}$$

Level 2

$$a_{0ij} = b_{000} + b_{101} * tx + V_{0ij} \tag{5}$$

$$a_{1ij} = b_{100} + b_{101} * tx + V_{1ij} \tag{6}$$

$$a_{2ij} = b_{200} + b_{201} * tx + V_{2ij} \tag{7}$$

$$tx = \sum_{q=1}^{c} \theta_q x_{iq} + \sum_{l=1}^{d} \mu_l z_{ijl} \tag{8}$$

$$\text{with} \quad \begin{pmatrix} V_{0ij} \\ V_{1ij} \\ V_{2ij} \end{pmatrix} \sim \text{N} \begin{pmatrix} 0 & \gamma_{00}^2 & 0 & 0 \\ 0, & 0 & \gamma_{10}^2 & 0 \\ 0 & 0 & 0 & \gamma_{20}^2 \end{pmatrix}$$

In level 0, y_{ij} is the observed CDR SUM score for subject i at time j. Term β_{0ij} is the random intercept, and β_{1ij} and β_{2ij} are the random individual slope of the linear term t_{ij} and the quadratic term t_{ij}^2 at time j. Term t_{ij} is the duration since onset of cognitive decline for subject i at time j. The term ε_{ij} represents the within-patient variation.

In level 1, the random intercept and random slope are divided into two parts, a and U (effect of time and residuals). In level 2, term x_{iq} is a c-dimension time-constant covariance matrix for subject i. Term $z_{ijl}$is a d-dimension time-varying covariate matrix for subject i at time j. It includes all of the changing features of subject i at time j. θ_q and μ_l are corresponding parameters for terms x_{iq} and z_{ijl}. V_{0ij}, V_{1ij}, and V_{2ij} are residuals that have variances of γ_{00}^2, γ_{10}^2, and γ_{20}^2, respectively. This ML model structure incorporates factors in a manner that accounts for errors at each level. It also determines the impact of the level 1 factor and level 2 factors on individual observations. Furthermore, it controls the specification of the covariance matrix for the residuals.

2.3. Semiparametric mixed-effects model

The semiparametric modeling method has increasingly been used to capture subtle changes in longitudinal data. In many regression models, an assumption of normality is needed. However, in the SME model, ordinal variables, even with small sample sizes, can be fitted in nonparametric models. In addition, the normality assumption is not required.

The effect of time and other covariates on the CDR SUM score (the response) is complicated. Nonlinearity itself cannot fully explain the heterogeneous shape of trajectories. Therefore, the penalized spline approach and its mixed-model representation is a good solution for featuring individual profiles. We assume that CDR SUM score, the response variable y_{ij} in Equation (9), is the combination of $f(t)$, linear expression of fixed effects of x_{iq} and z_{ijl}, and measurement error ε_{ij}. We will discuss two different scenarios based on within-patient correlation assumption. Equation (9) is the first case, an SME model without within-patient correlation, assuming CDR SUM scores

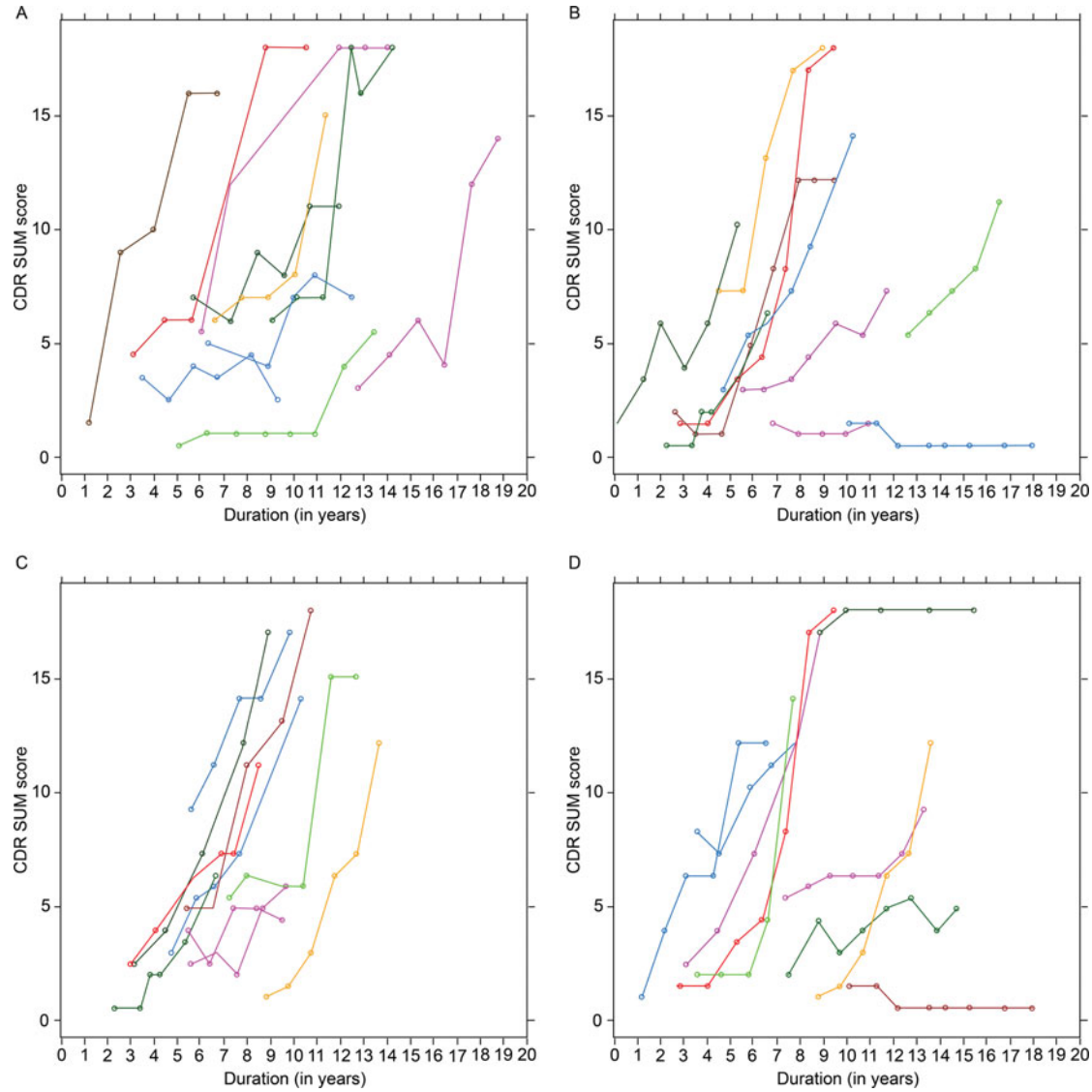

Figure 1. (A, B, C, and D). Forty individual CDR SUM score trajectories. Each figure is a plot of 10 patients' CDR SUM score records. Each colored line represents an individual patient's trajectory. This figure was randomly generated from the 2669 patients' records in training data, obtained from the NACC database in September 2015. The x-axis represents the duration since cognitive decline onset; the y-axis represents the CDR SUM score.

from the same patient are independent. We define the measurement error ε_{ij} following a normal distribution with standard variance σ_ε^2.

$$y_{ij} = f(t) + \sum_{q=1}^{c} \theta_q x_{iq} + \sum_{l=1}^{d} \mu_l z_{ijl} + \epsilon_{ij}$$
$$\epsilon_{ij} \sim N\left(0,\ \sigma_\varepsilon^2\right) \tag{9}$$

Similar to the definition in Equation (8), term x_{iq} is a c-dimension time-constant covariance matrix for subject i. Detailed variables in this study will be discussed in Section 3.1. θ_q and μ_l are the coefficients for terms x_{iq} and z_{ijl}. Term $f(t)$ is a penalized spline smooth function that reflects the overall trend of the CDR SUM score with time, as shown in Equation (10):

$$f(t) = \beta_0 + \beta_1 t + \beta_2 t^2 + \sum_{k=1}^{K} u_k (t - \kappa_k)_+^2$$
$$t < \kappa_1 < \kappa_2 < \cdots < \kappa_K < \max(t) \tag{10}$$

where β_0, β_1, and β_2 are the coefficients for intercept, linear, and quadratic terms, respectively. In Equation (10), u_k refers to the weight of each linear function, and $(t - \kappa_k)_+$ refers to the k^{th} linear function with a knot at κ_k. The number of knots K is fixed and large enough to ensure the flexibility of the curve. $\kappa_1 \ldots$, κ_K are a set of distinct fixed knots ranging from t to max(t), where t is the whole sample of years since onset. The knots were chosen as quantiles of t with probabilities 1/(K+1), …, K/(K+1). The method used to select the number of knots and the codes associated with selection have been documented by Ruppert (2002) and Durbán *et al.* (2005). We use truncated lines as the basis for regression:

$$(t - \kappa_k)_+ = \begin{cases} t - \kappa_k & : if\ t - \kappa_k > 0 \\ 0 & : if\ t - \kappa_k \le 0 \end{cases} \tag{11}$$

Referring to Equation (10), the basis of the spline model for $f(t)$ is

$$[1\ t\ t^2\ (t - \kappa_1)_+ \ \ldots\ (t - \kappa_K)_+\ (t - \kappa_1)_+^2\ \ldots\ (t - \kappa_K)_+^2\ ] \tag{12}$$

In Equation (9), which represents SME model with uncorrelated random effects, we assume that the observations within the subject i are independent. However, for longitudinal data, it is possible that observations of the same subject may correlate with each other along time points. This is the second scenario, the SME model with correlated random effects. The term ε_{ij} in Equation (9) no longer represents random variation; instead, it reflects the within-subject variation, comprising an exponential correlation function $\delta_i(t_{ij})$ and measurement error ω_{ij}, as shown in Equation (13):

$$f(t) = \beta_0 + \beta_1 t + \beta_2 t^2 + \sum_{k=1}^{K} u_k (t - \kappa_k)_+^2$$
$$\epsilon_{ij} = \delta_i(t_{ij}) + \omega_{ij} \tag{13}$$

where $\omega_{ij} \sim N(0, \sigma_\omega^2)$. The distribution of $\delta_i(t_{ij})$ follows a multivariate normal density with mean 0 and variance-covariance matrix Σ.

$$\delta_i(t_{ij}) \sim MVN\left(0, \sum\right) \tag{14}$$

Additionally, $\delta_i(t_{ij})$ follows an exponential correlation function $\rho(\Delta t)$.

$$\rho(\Delta t) = Corr(\delta_i(t_0), \delta_i(\Delta t + t_0)) = e^{\left(-\frac{|\Delta t|}{\tau}\right)} \tag{15}$$

where τ is the rate of decay for the correlation function for time between observations of $|\Delta t|$. $\rho(t)$ allows for observations further apart in time to have a reduced correlation. Term ω_{ij} is the residual component.

In the following, we have defined the SME model with uncorrelated random effects as the SME(N-cor) model and the SME model with correlated random effects as the SME(w-cor) model.

3. Results

3.1. Model application and evaluation

The goals of this study were to identify the influential factors that can predict CDR SUM scores and to develop a robust model to make predictions from existing patient profiles. We made assumptions that certain factors are associated with the course of decline and that patients who share the same profile would have a similar developmental trajectory. Univariate regression smoothing and a least-square means comparison were used to examine if the candidate variables were significant enough to build the model.

Our study examined 20 risk factors that were identified in previous medical literature (Fig. 2). The time-constant variables include duration since the onset (time), sex, years of education, and onset age. The time-varying variables are vascular health conditions and neuropsychiatric symptoms. These factors are also available in the NACC UDS database. Duration, education level, and onset age are derived variables that were created from the dataset. Vascular health conditions included heart attack/cardiac arrest, transient ischemic attack, atrial fibrillation, stroke, and diabetes. The neuropsychiatric symptoms covered 12 domains: delusions, hallucinations, agitation, depression, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability, aberrant motor behavior, nighttime behavior, and changes in appetite or the consumption of certain foods.

Although there is a tendency to perform trajectory studies for different dementia types, such as AD, Lewy body dementia, and Parkinson's dementia, we did not consider the diagnosis of dementia type as a parameter in the current study. The first reason for this is that the diagnostic methods are not sufficiently accurate to classify patients with enough precision to carry out a study based on diagnostic results. In medical diagnoses, sensitivity and specificity measure the ability to identify those with the

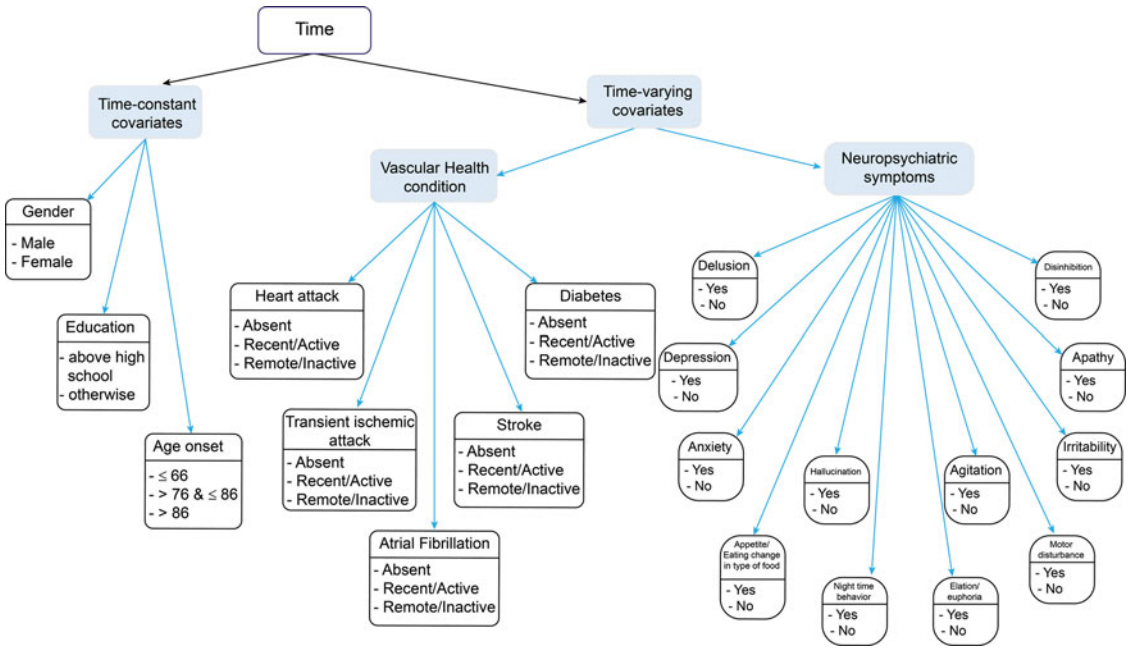

Figure 2. Levels of factors associated with the CDR SUM score in the present study. Note: The first-level factor is time, the second-level factors are time-constant factors and time-varying factors, and the lower branches are 20 factors with the NACC codes.

Table 1. Characteristics of selected patients from NACC database data between September 2005 and September 2015.

Patient characteristics	Age of onset			Total *N* (%)
	Young (≤ 66 y)	Middle (66 to 86)	Old (> 86 y)	
Gender (Male, %)	559 (64.25%)	978 (58.67%)	58 (43.94%)	1595 (59.76%)
Education level ≥ 12 y, %	831 (95.52%)	1536 (90.91%)	120 (92.14%)	2487 (93.18%)
Vascular health conditions, N *(%) of disease absence*				
CVHATT = 0	810 (93.1%)	1451 (87.04%)	120 (90.91%)	2381 (89.21%)
CVAFIB = 0	813 (93.45%)	1344 (80.62%)	104 (78.79%)	2261 (84.71%)
CBSTROKE = 0	817 (93.91%)	1460 (87.58%)	107 (81.06%)	2384 (89.32%)
CBTIA = 0	815 (93.68%)	1436 (86.14%)	108 (81.82%)	2359 (88.39%)
DIABETES = 0	779 (89.54%)	1409 (84.52%)	121 (91.67%)	2309 (86.51%)
Neuropsychiatric symptoms during the last visit, N *(%) of symptom absence*				
DEL = 0	690 (79.31%)	1308 (78.46%)	116 (87.88%)	2114 (79.21%)
HALL = 0	702 (80.69%)	1411 (84.64%)	117 (88.64%)	2230 (83.55%)
AGIT = 0	458 (52.64%)	979 (58.73%)	97 (73.48%)	1534 (57.47%)
DEPD = 0	535 (61.49%)	1086 (65.15%)	92 (69.7%)	1713 (64.18%)
ANX = 0	462 (53.1%)	1027 (61.61%)	105 (79.55%)	1594 (59.72%)
ELAT = 0	786 (90.34%)	1588 (95.26%)	128 (96.97%)	2502 (93.74%)
APA = 0	335 (38.5%)	748 (44.87%)	85 (64.39%)	1168 (43.76%)
DISN = 0	569 (65.4%)	1306 (78.34%)	114 (86.36%)	1989 (74.52%)
IRR = 0	539 (61.95%)	1037 (62.21%)	100 (75.76%)	1676 (62.80%)
MOT = 0	490 (56.32%)	1211 (72.65%)	121 (91.67%)	1822 (68.27%)
NITE = 0	502 (57.7%)	1045 (62.69%)	91 (68.94%)	1638 (61.37%)
APP = 0	504 (57.93%)	1139 (68.33%)	102 (77.27%)	1745 (65.38%)
Total *N* (%)	870 (32.6%)	1667 (62.46%)	132 (4.95%)	2669 (100%)

Note: Codes for gender: Female = 2; Male = 1. Abbreviations: CVHATT: heart attack/cardiac arrest; CBTIA: transient ischemic attack; CVAFIB: atrial fibrillation; CSTROKE: stroke; DIABETES: diabetes; DEL: delusions; HALL: hallucinations; AGIT: agitation; DEPD: depression; ANX: anxiety; ELAT: elation/euphoria; APA: apathy/indifference; DISN: disinhibition; IRR: irritability; MOT: aberrant motor behavior; NITE: Nighttime behavior; APP: appetite/eating change in type of food.

disease correctly (true positive rate) and those without the disease (true negative rate). A study by Beach *et al.* (2012) reported that the sensitivity in the diagnosis of AD ranged from 70.9% to 87.3%, and specificity ranged from 44.3% to 70.8% for NACC data. Clark *et al.* (2011) reached a similar conclusion, stating that 10% to 20% of patients clinically diagnosed with AD did not have AD pathology. The presence of mixed dementia is another factor that makes diagnosis difficult, because of the coexistence of more than one neuropathology. A sample study by Schneider *et al.* (2007) showed that, among community-dwelling older individuals with dementia, 54% showed pathological evidence of one or more coexisting dementias. All of these factors make it difficult to make rigorous diagnoses. The inclusion of the heterogeneous cognitive decline patients would add variance to the models, but would help to access a more general cognitive decline trajectory that does not need specific diagnoses.

3.2. Data exploration

In the training data, the mean of duration from age of onset to death was 8.2 y (standard deviation = 3.9 y; range = 0.2 to 39.3 y). The mean age of onset (first appearance of cognitive decline symptoms) was 70.4 y (standard deviation = 10.8 y; range of onset age = 29 to 103 y). Table 1 shows the patient characteristics at three levels of onset age—young (≤ 66 y), middle (> 66 y and ≤ 86 y), and old (> 86 y)—including sex, educational level, vascular health condition, and neuropsychiatric symptoms.

3.3. Model fitting and selection

The variables were tested in a univariate analysis, which is a univariate regression on the CDR SUM scores over all the patients in the training data. Those factors significant in a least-square means *t*-test were entered into the model. In addition to the 20 variables shown in Fig. 2, three second-level interaction terms were included (duration × onset age, duration × gender, and duration × education level). Other interaction terms are not statistically significant ($p > 0.05$) with minimal coefficient factors; furthermore, other interactions have no medical report supporting their effect on cognitive decline. Therefore, we eliminate other interaction terms after preliminary fitting of the complete models. To obtain less biased estimates of the variance terms, restricted maximum likelihood was used in model fitting. Since the CDR SUM score is a psychometric scale, floor and ceiling effects corresponded to the minimum and maximum scores obtainable (0–18). Predicted values smaller than 0 and larger than 18 were therefore truncated to be 0 and 18, respectively. In order to examine the goodness-of-fit of the two types of modeling methods, model selection criteria must be directly comparable between different models, and be interpretable in terms of the information content of the data. Therefore, Nakagwa and Schielzeth's R^2_{GLMM} (Nakagawa and Schielzeth, 2013) is preferred to Information Criteria, namely AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion). AIC and BIC were widely used as model selection criteria. However, they do not provide information about the absolute model fit and variance explained by a model (Nakagawa and Schielzeth, 2013). Marginal R^2 and Conditional R^2 in Nakagwa and Schielzeth's R^2_{GLMM} are dimensionless, and have intuitive interpretation, and values from different models are comparable. Marginal R^2 ($R^2_{GLMM(m)}$) evaluates the percentage of variance explained by fixed factors and is defined as Equation (16). Conditional R^2 ($R^2_{GLMM(c)}$) evaluates the percentage of variance explained by

Table 2. Model fit and parameter estimates, CDR SUM score in NACC data, September 2005 to September 2015.

	SME (N-cor) Model			
			95% CI	
Parameter	Estimate	*p*-value	Lower	Upper
(Intercept)	2.59	0	1.56	3.63
DURATION	0.03	0.83	− 0.24	0.3
I(DURATION^2)	0.07	0	0.06	0.08
Age of onset: Old	− 0.74	0.03	− 1.4	− 0.08
Age of onset: Young	0.45	0.07	− 0.04	0.93
Education level ≥12 y	− 1.42	0	− 2.22	− 0.63
SEX	0.22	0.3	− 0.19	0.63
CVHATT	− 0.12	0.06	− 0.25	0.01
CVAFIB	− 0.05	0.39	− 0.15	0.06
CBSTROKE	0.15	0	0.05	0.25
CBTIA	− 0.07	0.06	− 0.14	0
DIABETES	0.01	0.96	− 0.24	0.25
DEL	0.91	0	0.71	1.1
HALL	1.36	0	1.13	1.59
AGIT	0.54	0	0.39	0.69
DEPD	− 0.25	0	− 0.39	− 0.1
ANX	0.29	0	0.14	0.43
ELAT	0.11	0.44	− 0.18	0.4
APA	0.8	0	0.66	0.94
DISN	0.21	0.01	0.05	0.38
IRR	− 0.44	0	− 0.59	− 0.3
MOT	1.08	0	0.92	1.24
NITE	0.23	0	0.09	0.37
APP	0.62	0	0.47	0.76
DURATION: Age of onset: Old	0.2	0.06	− 0.01	0.42
DURATION: Age of onset: Young	− 0.02	0.68	− 0.14	0.09
DURATION: SEX	0.17	0	0.07	0.28
DURATION: Education level ≥ 12 y	0.17	0.09	− 0.03	0.38

Abbreviations: CVHATT: heart attack/cardiac arrest; CBTIA: transient ischemic attack; CVAFIB: atrial fibrillation; CSTROKE: stroke; DIABETES: diabetes; DEL: delusions; HALL: hallucinations; AGIT: agitation; DEPD: depression; ANX: anxiety; ELAT: elation/euphoria; APA: apathy/indifference; DISN: disinhibition; IRR: irritability; MOT: aberrant motor behavior; NITE: Nighttime behavior; APP: appetite/eating change in type of food.

the entire model and is defined as Equation (17). The other measurement is Pearson correlation coefficient r between the fitted and the observed values as Equation (18). It measures the strength and direction of the linear relationship between the fitted and observed values. The higher the correlation, the better the fitted values from a given model simulate the observed value.

$$R^2_{GLMM(m)} = \frac{\sigma_f^2}{\sigma_f^2 + \sum \sigma_l^2 + \sigma_e^2 + \sigma_d^2} \tag{16}$$

$$R^2_{GLMM(c)} = \frac{\sigma_f^2 + \sum \sigma_l^2}{\sigma_f^2 + \sum \sigma_l^2 + \sigma_e^2 + \sigma_d^2} \tag{17}$$

$$r = \frac{n\left(\sum y_{obs} * y_{fit}\right) - \left(\sum y_{obs}\right)\left(\sum y_{fit}\right)}{\sqrt{\left[n\sum y_{obs^2} - \left(\sum y_{obs}\right)^2\right]\left[n\sum y_{fit^2} - \left(\sum y_{fit}\right)^2\right]}} \tag{18}$$

where σ_f^2 is the variance of fixed effects in the model, σ_l^2 is the variance of the lth random factor,σ_e^2 is additive dispersion variance, and σ_d^2 is distribution-specific variance (Nakagawa and Schielzeth, 2010). y_{obs} are the observed CDR SUM scores, and y_{fit} are the fitted values by the proposed models. Analysis was implemented in R software (version 3.2.5; R Foundation for Statistical Computing, Vienna, Austria).

The SME(N-cor) model had Pearson correlation coefficient r of 0.93, marginal R^2 of 0.41, and conditional R^2 of 0.96. The SME(w-cor) had Pearson correlation coefficient r of 0.73, marginal R^2 of 0.44, and conditional R^2 of 0.64. The ML model had a correlation coefficient of 0.52, marginal R^2 of 0.47, and conditional R^2 of 0.87. Among all three model selection indicators, the SME(N-cor) model outperformed the other two models. Although the predicted values by ML model had remarkably higher marginal and conditional R^2 than by SME(w-cor), indicating the larger proportion of the variance explained by both fixed effects and the entire model, the correlation coefficient between observed values and predicted values was only 0.52, which is the lowest among the three models. The SME model without the random effects correlation fit the training data remarkably well, with a correlation of 0.93 between the fitted and observed values. The hypothesis that the CDR SUM score within the same subject would have an exponential correlation was not supported. The residual plot for the SME(N-cor) model was approximately normally distributed, indicating that the model is adequate. Therefore, the SME(N-cor) model was preferred over the SME(w-cor) model and the ML model, and was selected for prediction. The parameters in the SME(N-cor) model are listed in Table 2.

3.4. Testing the model for validation

To test if the model was robust, 5000 observations were randomly drawn 10 times from the test data pool and entered into both SME models. Pearson correlation between the predicted CDR SUM by the SME(N-cor) model and observed CDR SUM was assessed. The results were stable, and again, the prediction from the SME(N-cor) model was significantly better than

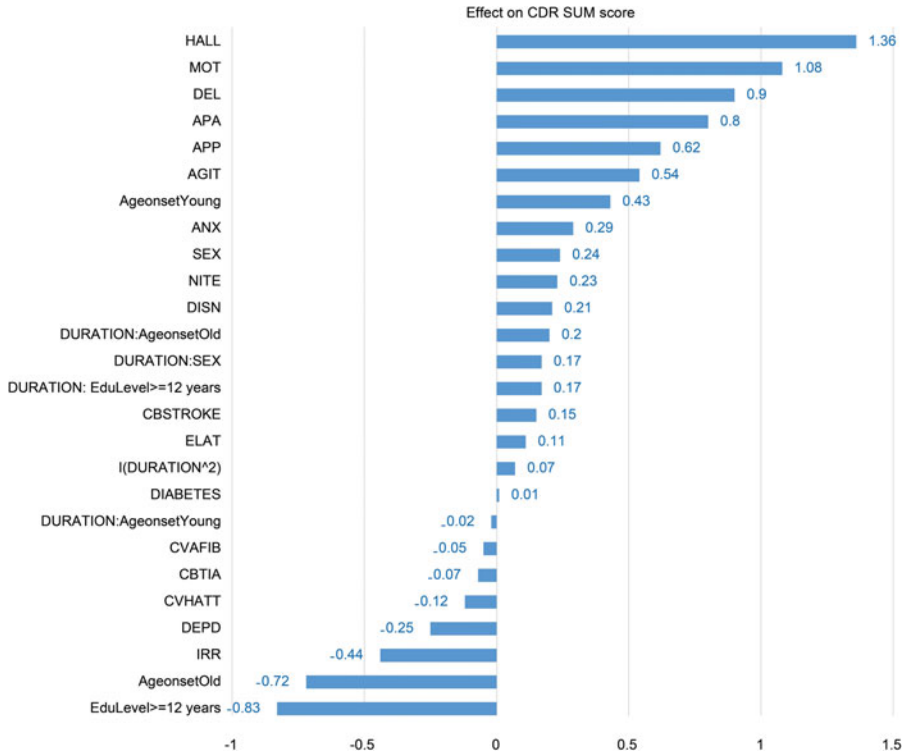

Figure 3. The effect of each influential factor in the SME(N-cor) model. Variables in the model are presented in the left-hand column; the blue bars represent the influence of the factor on the CDR SUM score; the numbers on the right side of the bar are the estimated coefficients of the factors. Abbreviations: CVHATT: heart attack/cardiac arrest; CBTIA: transient ischemic attack; CVAFIB: atrial fibrillation; CSTROKE: stroke; DIABETES: diabetes; DEL: delusions; HALL: hallucinations; AGIT: agitation; DEPD: depression; ANX: anxiety; ELAT: elation/euphoria; APA: apathy/indifference; DISN: disinhibition; IRR: irritability; MOT: aberrant motor behavior; NITE: nighttime behavior; APP: appetite/eating change in type of food.

from the SME(w-cor). The mean of the correlation between the predicted CDR SUM from SME(N-cor) and the observed CDR SUM was 0.41 (variance of 9.50×10^{-5}). The mean of the correlation between the predicted CDR SUM from SME(w-cor) and the observed CDR SUM was 0.39 (variance of 3.16×10^{-5}). Furthermore, the Mean Squared Errors (MSE) calculated for the SME(N-cor) model and SME(w-cor) model were 55.93 (variance of 107.62) and 65.12 (variance of 131.47), respectively. The higher correlation and smaller MSE are the substantial evidence of higher-quality prediction from the SME(N-cor) model than its counterpart.

Although the correlation was moderately positive, it can be considered as a strong correlation in a human-related study. It should be kept in mind that correlation coefficients are very sensitive to outliers. Therefore, the SME(N-cor) model was considered as representative of typical dementia progression processes, and it was selected for further analysis. Fig. 3 illustrates the magnitude of the estimated coefficients for the SME(N-cor) model. Fig. 4 is the estimated coefficients of the SME(N-cor) model in a sorted order.

Neuropsychiatric symptoms, including delusion, hallucination, agitation, anxiety, apathy, motor disturbance, and appetite change, were all indicators of higher CDR SUM scores. History of stroke, presence of disinhibition, and nighttime behavior disturbances (awakening during the night, rising too early, or taking excessive naps during the day) were also associated with higher CDR scores, but to a lesser extent. Furthermore, along with duration, females showed higher CDR SUM scores than their male counterparts. This could be the result of a longer survival time for females.

An older onset age (>86 y), higher level of education (≥12 education years), and presence of irritation were indicators of a lower CDR SUM score. Education level was the most influential

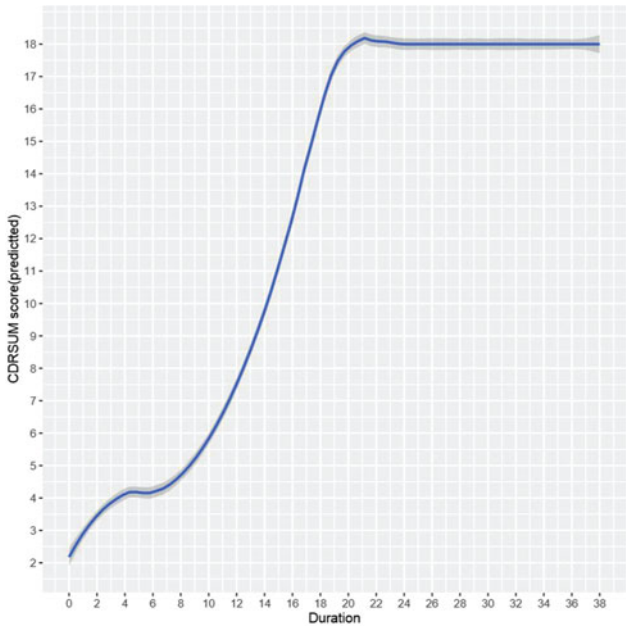

Figure 4. Point estimation of nonparametric penalized spline smooth function *f*(*t*) obtained from SME(N-cor) model for patients in NACC UDS data from September 1, 2005, to September 1, 2015. The x-axis represents the duration (in years) since cognitive decline onset; the y-axis represents the CDR SUM score. A 95% confidence interval lies in the grey range area.

factor among these three. Depression had a minimal negative effect on the CDR SUM score.

Among the factors we tested in the SME(N-cor) model, the statistically non-significant factors were young onset age ($\leq$66 y), sex, heart attack/cardiac arrest, atrial fibrillation, transient ischemic attack, diabetes, the presence of elation, an interaction between duration and onset age, and an interaction between duration and education level. For these factors, we found a likelihood exceeding 95% that these factors had no effect on the CDR SUM prediction outcome. The performance of the model would decrease by 50% if the categorical factor of APOE $\varepsilon 4$ presence was added into the model. This could be because the distribution of APOE $\varepsilon 4$ alleles in the training data is not consistent within the population and caused overfitting of the model. Furthermore, this also agrees with the conclusion that APOE $\varepsilon 4$ does not significantly influence the patterns of dementia progression (Kleiman *et al.*, 2006; Cosentino *et al.*, 2008; Wilkosz *et al.*, 2009).

3.5. CDRSUM prediction outcome and examples

The trajectory of the CDR SUM score differed according to model type. The semiparametric model gives an estimation of CDR SUM score by combining the penalized spline smooth function of time and the additive effect of other covariates. The nonparametric penalized spline smooth function $f(t)$ reflects the overall trend of CDR SUM score with time. Fig. 4 is the point estimation of $f(t)$obtained from the SME(N-cor) model for patients in NACC UDS data from September 1, 2005, to September 1, 2015. The curve shows that the general trend of increasing CDR SUM score with time, whereas from year 4 to year 8 there is a steady period followed by a rapid increasing trend again. After year 20, the CDR SUM score stabilized at 18 points, which is the ceiling level of the CDR SUM score scale. The estimation of CDR SUM score is made based on $f(t)$ and the fixed and random effects in the SME(N-cor) model.

In order to visualize the estimation of the CDR SUM score trajectory, we randomly selected four patients from the training data pool and plotted the actual CDR SUM score recorded in NACC UDS data and the predicted CDR SUM score by SME (N-cor) model (Fig. 5). The MSE for predicted and actual CDR SUM score is 2.475 for the 14-point estimation in total. The SME(N-cor) model gave a reasonably good estimation of the CDR SUM score trajectory. The predicted CDR SUM score for the last visit in Fig. 5 (D) had a slight drop because of drug intervention on agitation and anxiety. The psychiatric symptoms were suppressed; thus, their non-existence decreased the CDR SUM score. Besides therapeutic intervention, it should be noted that both environmental and lifestyle factors, such as diet, physical activities, and social connection, can play a role in cognitive decline progression. Therefore, adjustment of prediction results should be made depending on individual cases in a practical model application.

4. Discussion

In order to simulate and estimate the individual trajectory of cognitive decline in dementia, we used multi-level polynomial regression and semiparametric methods, respectively. Instead of using Information Criterion, we applied Nakagawa and Schielzeth's R^2_{GLMM} and Pearson correlation coefficient between fitted and observed value as criteria for model selection. Nakagawa and Schielzeth's R^2_{GLMM} represents the goodness of fit and has an intuitive interpretation of the proportion of variance explained by fixed effects and the entire model. Pearson correlation coefficient gives a direct measurement of the linear correlation between fitted and observed CDR SUM scores, which is interpretable and can be compared among results from different modeling techniques.

The semiparametric model without correlation characterized the patient features that influence the rate of cognitive decline and provided a quantitative description of the trajectory of cognitive decline with significant accuracy. Our study revealed that the progression of dementia can be predicted using demographic and clinical characteristics of patients. Both SME models (with and without correlation) had a better fit and yielded better prediction results than the ML model. The prediction results of these two SME models showed that avoiding incorporation of longitudinal correlation improved prediction accuracy. The SME(N-cor) model was selected as a reliable tool for estimation of the CDR SUM in relation to cognitive decline. Moreover, the model can potentially be applied to clinical monitoring, dementia prognosis, and reference for medical trials, as patient-specific trends can be obtained.

4.1. Findings in the context of the literature

Our study findings support the conclusions of the Cache County Dementia Progression Study (Tschanz *et al.*, 2011); namely, that a lower level of education and at least one clinically significant neuropsychiatric symptom at baseline are predictive of a shorter time to the progression to severe dementia. Moreover, we identified that the presence of elation does not necessarily produce a higher CDR SUM score. Our results also support the finding that higher education levels are associated with lower CDR SUM scores (Chaves *et al.*, 2010). This could represent support for the cognitive reserve hypothesis, whereby patients with dementia and higher educational status have a higher cognitive reserve and, thus, a slower cognitive decline (Evans *et al.*, 1993; Letenneur *et al.*, 1994; Stern, 1994, 2012; Stern *et al.*, 1995). Our findings also indicated that stroke has a modest impact on fast cognitive decline (Solfrizzi *et al.*, 2004). Ott *et al.* (1999) claimed that patients with diabetes have a higher risk of dementia; however, diabetes was not associated with higher CDR SUM scores in the present study. This could be because diabetes is only a risk factor for dementia, and not for its faster progression.

The semiparametric method in our study combined penalized regression splines and mixed-effects modeling, which provide individualized approximations of nonlinear estimation while preventing over-fitting. It is, therefore, able to capture subtle changes and is more accurate than the mixed model used in the Cache County Dementia Study (Tschanz *et al.*, 2011). Indeed, our SME model produced a more elaborate curve fit than its ML counterpart. Furthermore, we found no evidence of a correlation between CDR SUM scores of the same subject. This suggests that the CDR SUM scores at different time points are independent of each other, and that the influence of time

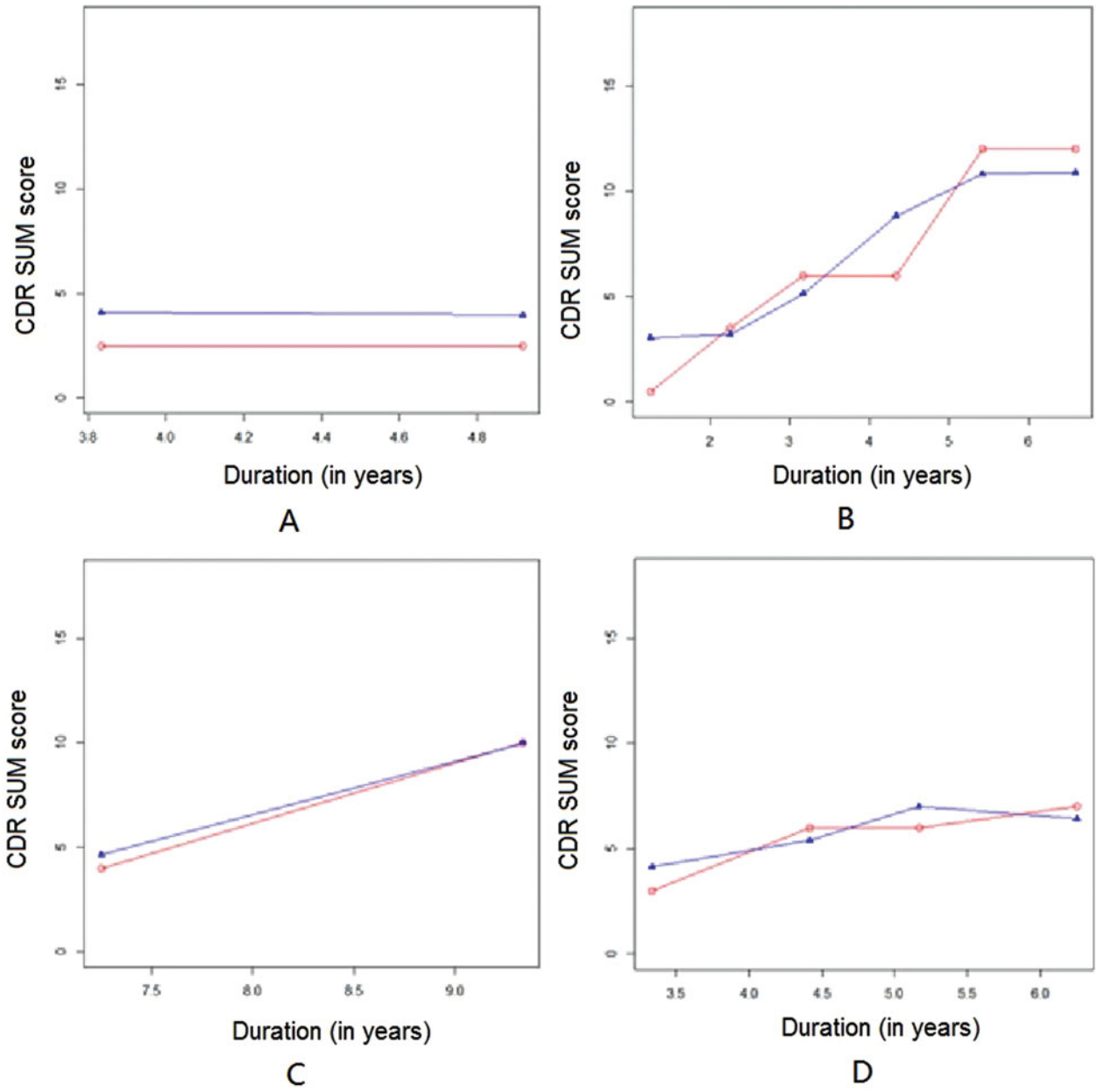

Figure 5. (A, B, C, and D). The prediction results for four randomly selected patients in training data. Red circles are the actual observed CDR SUM score, and blue triangles are the predicted values by SME(N-cor) model. The x-axis represents the duration (in years) since cognitive decline onset; the y-axis represents the CDR SUM score.

on future scores cannot be predicted by previous scores. The SME(N-cor) model achieved a 93% correlation of observed and predicted values. We have, therefore, demonstrated the reliable performance of this model in the prediction of test data, which is of high referential value in prognosis. With further population-based studies, more generalized conclusions can be made about the SME model.

4.2. Limitations

Several limitations of this study should be considered when interpreting the results. First, the samples were recruited based on clinic visits. Therefore, there may have been a sampling bias compared to population-based studies. It may also be more likely that these patients were living with family or friends, had a greater educational/professional attainment, or more awareness of cognition impairment. Second, our study did not assess the impact of some potentially important factors on disease progression, such as drug intake, lifestyle, social network support, treatment, and quality of care received. Therefore, overall individual cases are important in CDR SUM score prediction and should be considered as supplementary information in prediction. Third, our model did not consider the reversion of cognitive/functional ability (Koepsell and Monsell, 2012). In future studies, a sub-model would be better to represent the trajectory for individuals who experience reversion. Finally, since pathological evidence from a biopsy study showed a slower rate of cognitive and functional decline in patients with mixed AD with vascular dementia compared to mixed AD with Lewy body pathology (Pillai *et al.*, 2015), a high accuracy of diagnosis in future studies would help to improve the model and gain understanding about the characteristics of the progression patterns of different types of dementia.

4.3. Conclusion

The semiparametric approach is quite strong in modeling the trajectory of cognitive decline in dementia. Our SME model characterized patient features that influence the rate of cognitive decline, and provided a quantitative description of cognitive decline trajectory with a high accuracy. While some other potentially important factors may affect the CDR SUM score, such as drug intake, lifestyle, social network support, treatment, and quality of care received, the model built in this study can serve as a baseline model for physicians' reference and can be used to indicate individual prognoses of the progression of cognitive decline. This approach is also of great value to explain and predict outcome variables in other longitudinal studies, especially of time-series data that record time-based behavior, such as other chronic disease registries and medical trials.

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