A SEMIPARAMETRIC TRAJECTORY MODEL FOR COGNITIVE DECLINE

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ABSTRACT

Dementia is a group of diseases that are caused by neurocognitive disorder. It is the second leading cause of death in older adults in the US. People who suffer from dementia experience memory loss and other cognitive or functional decline that is severe enough to interfere with their professional and social performance. In spite of the controversy on accuracy of diagnosis and debate on disclosure of dementia diagnosis results, it is important for patients and their families to know what to expect about the future development of cognitive decline.

The course of dementia progression is highly diverse, and the symptoms vary differently from case to case. Amnesia, aphasia, agnosia, and apraxia can exist solely or in combination. The rate of cognitive decline, in the term of Clinical Dementia Rating Score, demonstrated different patterns on an individual level. However, in spite of the variety of symptoms, it is essential to map the cognitive decline to the severity of the impact of the symptoms on daily life.

Clinical Dementia Rating SUM score (CDR SUM score) is a comprehensive evaluation based on cognition level. Trajectory modeling can provide a practical tool for physicians to make prognosis and medical trials. Furthermore, trajectory modeling can be a valuable reference for stakeholders to use in reimbursement decisions or policies on caregiving resource allocation. However, there is a gap in the current research to predict the trajectory for cognitive decline. In this research, we studied the typical pattern of CDR SUM scores and predicted a timeline for people with cognitive decline. The innovation and significance of this study is the development of multilevel and semiparametric models, and a simple and straightforward criterion for model evaluation and selection. The model we built showed robustness in both explaining the data and predictions. The study results revealed the factors associated with cognitive decline rate in terms of CDR SUM score, and gave implications on accurate CDR SUM score prediction by individual

demographic and clinical profiles. The developed model can also be applied to other longitudinal studies in behavioral science, medical monitoring, and other time series related studies.

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DEDICATION

To all those who supported and encouraged me in my study at NDSU.

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LIST OF ABBREVIATIONS

MCI.....Mild Cognitive Impairment

AD .....Alzheimer's disease

ADL .....Activity of daily living

APOE ε4 .....Apolipoprotein epsilon 4

CDR .....Clinical dementia rating

IADL .....Instrumental activities of daily living

LBD.....Lewy bodies dementia

NACC .....National Alzheimer's Coordination Center

ML.....Multilevel model

SME (w-cor) .....Semiparametric model with correlation

SME (N-cor) .....Semiparametric model without correlation

CHAPTER 1. INTRODUCTION OF DEMENTIA AND COGNITIVE DECLINE

1.1. Dementia, Diagnosis and MCI

In this section, we have a brief overview of facts on Dementia, related cognitive disorders, and the diagnosis facts of dementia. Finally, we would identify cognitive decline as the research objective of this study.

Dementia is a devastating disease that prevails in the aged population. People with dementia experience loss of cognitive function, which includes loss of the ability to think, remember, reason, and even behavioral abilities (National Institutes of Health, 2013) to an extent that it interferes with one's social or occupational functions. There are several types of dementia, and it is not uncommon for people who suffer from dementia to have coexistence of more than one neuropathology, which is known as mixed dementia. Alzheimer's disease is the most common dementia type, accounting for 60 to 80 percent of the cases. It is reported that about 11% of people aged 65 and older have Alzheimer's disease, and there is a higher risk (32 %) among those who are age 85 and older (Alzheimer's Association, 2015).

Diagnosis standards are established for the diagnosis of Alzheimer's disease, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5®) (American Psychiatric Association, 2013), the National Institute of Neurologic and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's disease and Related Disorders Association(ADRDA) criteria. NINCDS and ADRDA criteria are more specific about mental status testing and neuropsychological tests. The essential features of diagnosis include (1) memory impairment and (2) at least one impairment in language, executive function, or recognition. In addition, these deficits must include a significant impairment in social or occupational functioning and make a significant decline from a previous level of performance. Furthermore, other psychiatric

disorders or neurological explanations for the decline are excluded. It is reported that the current accuracy of diagnosis is not very high based on the neuropathology golden standard for Alzheimer's disease. The sensitivity of diagnosis (true positives/ (true positives + false negatives)) ranges from 70.9 to 87.3%; the specificity of diagnosis (true negatives/ (true negative+ false positive)) ranges from 44.3 to 70.8% (Beach, Monsell, Philips & Kukull, 2012).

Early diagnosis of dementia is important for patients and their families to get support from professionals. A comprehensive evaluation that might include neurological tests, cognitive and neuropsychological tests, laboratory tests, and brain scans is necessary before a diagnosis of dementia can be made. However, no method has shown to have a high sensitivity or specificity except for the after mortal autopsy. The mechanism under dementia, such as morphologic features, amyloid pathology, neurofibrillary tangle pathology, and neuronal loss still remains largely unknown despite intensive studies. State of the art theories and neuro imaging technologies such as MRI (magnetic resonance imaging) and PET (positron emission tomography) have been developed in recent decades. For example, magnetic resonance microscopy (MRM) refers to very high resolution MRI imaging, which is magnetic resonance imaging (MRI) at a microscopic level down to the scale of 5 to 10 μm^3. These examination techniques enable better discrimination of the brain lesions. Other techniques such as CSF (cerebrospinal fluid) are also being introduced to aid more accurate diagnosis results.

In fact, the specific type of dementia may not be confirmed until a post mortal brain autopsy (National Institutes of Health, 2013). Autopsy studies of nearly 1,000 dementia patients at 30 top centers supported by the National Institute on Aging from 2005 to 2010 found that 17 to 30% of those diagnosed with Alzheimer's disease had been misdiagnosed and had other conditions (Alzheimer's Association, 2012). A study by Schneider, Arvanitakis, Bang, and

Bennett (2007) showed that among community-dwelling older people with dementia 54% have pathological evidence of one or more coexisting dementias.

Before the diagnosis of dementia, there is an insidious stage that is defined as Mild Cognitive Impairment (MCI). The term cognition encompasses processes such as attention, memory (involves encoding, storing, retaining and recalling information and experience), judgment and evaluation, reasoning and computation, problem solving and decision making, and comprehension and production of language. Cognitive decline is the impairment of the capacity to perform higher mental processes of reasoning, remembering, paying attention, understanding, and problem solving compared to one's normal performance. MCI is a condition in which an individual has mild but measurable changes in thinking abilities. The changes are noticeable to the person affected and to family members and friends, but do not affect the individual's ability to carry out everyday activities. This concept is rather heterogeneous with regard to its inclusion of a variety of types of cognitive dysfunction.

Amnesia MCI is the most common type of MCI and refers to memory only decline. Multi-dimensional MCI is the second most common type of MCI. MCI that affects thinking skills rather than memory is known as nonamnestic MCI. Non amnestic MCI patients may have only impairment in one single nonmemory cognitive domain such as language, executive function, or visuospatial skills. MCI does not always lead to dementia. Heterogeneity of MCI classifications result in different prevalence and conversion rates. In some individuals, MCI reverts to normal cognition or remains stable. According to a meta-analysis about reversible dementia by Clafield (2003), only 0.6% of dementia cases actually reversed (0.29% partially, 0.31% fully). Busse, Angermeyer, and Riedel-heller (2006) argued that up to 60% to 65% of individuals with MCI progress to dementia in their lifetimes.

Severe Alzheimer's dementia is defined as a Mini-Mental State Examination (MMSE) score of less than or equal to 10 or a Clinical Dementia Rating score of three (severe). If only the MMSE criteria were met, inclusion requires a Clinical Dementia Rating score of more than or equal to two (moderate); and if only Clinical Dementia Rating Scale criteria were met, severe Alzheimer's dementia inclusion requires a MMSE score of less than 16 (National Institute for Health and Care Excellence [NICE], 2006).

Cognitive ability and functional ability are two distinct aspects in dementia severity (Bruce,William, & Seab, 1989). MMSE is the most commonly used instrument for screening cognitive ability (de Boer, Mattace-Raso, van der Steen, & Pel, 2013). MMSE would not be accurate if the patient has linguistic communication or sensory disabilities. It is commonly agreed that MMSE scores of 27-30 out of 30 are considered normal cognition; 21-26 are mild decline, 10-20 are moderate, and less than 10 are severe impairment (National Institute for Health and Care Excellence [NICE], 2006). A study by Wilkoz et al., (2010) found there are six trajectories with significantly different courses indicated by rates of MMSE score decline in Alzheimer's dementia subjects. MMSE test is a fast and convenient tool not requiring any lab test or other information. However, it is limited in detecting subtle cognitive losses, particularly in well-educated patients (Spering et al., 2012) and needs to consider an allowance for ethnicity (Costa et al., 2013). Stroop-Vicotria test, Boston Naming test, and other tests are used in assessing discrete cognitive domains such as working memory and executive function (Cloutier, Chertkow, Kergoat, Gauthier, & Belleville, 2015).

However, cognitive ability alone gives little hint on the overall performance of a patient in daily life. Functional ability is another strong indicator of dementia severity. There is a correlation between cognitive ability and functional ability but they progress differently

(Mortimer, Ebbitt, Jun, & Finch, 1992; Dodge, Du, Saxton & Ganguli, 2006). Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) are significant indicators for functional ability. Several research results show that MMSE scores and functional performance scores are not significantly associated (Brown, Elliot and Fielding, 2014). MMSE scores can explain only about one-third of the variance in both ADLs and IADLs in the whole sample, and the MMSE and ADLs were independent of one another in half of less demented samples (Reed, Jagust, & Seab, 1989).

It is necessary to get an overall idea of how dementia progression would impact a patient's daily life. Clinical Dementia Rating (CDR) score is by far the most comprehensive indicator that gives practical information on how well a patient would adjust to one's life independently and a better understanding of one's cognition wellbeing. CDR was developed to evaluate the severity of dementia in the Memory and Aging Project at Washington University School of Medicine in 1979. In assigning a Global CDR score, six domains are scored respectively to construct the overall CDR table. The six domains are Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. It is a four-point scale: CDR-0 notes no cognitive impairment and CDR-3 is most severe stage of dementia. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member). In rating each of these domains, the assessment should be on the patient's cognitive ability to function in these areas. If they are limited in performing activities at home because of physical frailty, this should not affect their scoring on the CDR that again should be rated on their cognitive ability alone. The Clinical Dementia Rating Scale Sum of Boxes (CDR SUM) score is commonly used. It is much simpler to calculate than the global score which needs an algorithm

for computation. CDR SUM scores range from 0 to 18, and is the sum of the CDR score from each of the six domains.

1.2. Problem Statement

The rate of progression of dementia is highly variable. Some patients experienced fast cognitive deterioration and had a short survival time after cognitive decline onset, some patients maintained a constant cognitive level until death, and some patients had cognitive reversion back to normal and then impaired cognition again.

Although the rate of progression of dementia is highly variable and the pathology of dementia patients are heterogeneous, it is important to identify the patterns of dementia progression. Patients and their families need to know what to expect with regards to cognitive decline behavior, what level of severity would cognition and functional ability reach along with time, and how long would they survive. Those answers would be helpful for patients and their families to plan for management of the disease, the future finance, and other care arrangements. The study of progression course also facilitates planning of clinical trials for proposed treatments. Furthermore, the results of this study would help establish eligibility criteria for services, define a threshold for reimbursement that needs the information on the subject's functional ability evaluation, and provide a reference for government or other payers of medical cost.

In this research, we seek to uncover general laws and principles that govern dementia progression. We assume that certain factors are associated with the decline course and that patients who share similar profiles would have similar decline trajectories. The proposed models integrate the parametric families of probability distribution to estimate the underlying process of

cognitive decline. Through testing the viability of the proposed models, we select a best model to explain the observed change of interest and predict future cognitive states for the patients.

The CDR SUM score reflect the level that the cognitive decline affects a patient's standard of living. Therefore, it is a good indicator among many (such as MMSE) to study and use for prediction. The study samples are collected for patients of White race, with longitudinal data from Sep 2005 to Sep 2015, based on National Alzheimer's Coordination Center (NACC) database. We will identify the risk factors that are significant to CDR SUM score prediction; develop a series of prediction models in different strategies; and evaluate the models according to the model fitness.

There are two goals in this study. The first goal is to identify influential factors that can predict CDR SUM score. The second goal is to develop a robust trajectory model for predicting cognitive decline based on existing patient profiles. The procedure to accomplish the goals would be in eight steps: 1. State the problem of the proposing model to predict the CDR SUM score, 2. Select potentially relevant variables, 3. Training data preparation, 4. Specify possible models, 5. Fit the models, 6. Evaluate the models, 7. Use the chosen model to make an estimation for new data to test the robustness of the model, 8. Discuss the results and find future directions to make improvement.

The rest of the dissertation is organized as follows. In the next chapter we review previous work on factors associated with cognitive decline and the methods for trajectory modeling for cognitive decline. Chapter 3 contains six strategies that are proposed for trajectory modeling. Approaches were based on linear regression, polynomial regression, multilevel model, and semiparametric model and are presented in this chapter. Then model evaluation methods are introduced as two proposed criteria: R-squared and correlation coefficient. In Chapter 4, the

proposed trajectory modeling techniques are applied to data from NACC database. The selected model is tested using a different dataset to validate the model's robustness. In Chapter 5, we discuss the study findings and also point out the future research directions and application in practice for trajectory modeling for cognitive decline.

CHAPTER 2. LITERATURE REVIEW

There is considerable variability in progression rates among dementia patients (Doody et al., 2010). The reasons for, and the factors associated with, such different trajectories of cognitive functional decline severity remain largely unknown, yet some insight into this complex phenomenon could help identify high-risk groups.

2. 1. Factors Associated with Cognitive Decline

In past studies, factors that are frequently reported to indicate fast progression of cognitive decline include female gender (Tschanz et al., 2011; Li et al., 2014; Peters et al., 2015), shorter years of education (Shadlen 2005; Caamano-Isorna et al.,2006; Li et al., 2014; Peters et al., 2015), early-onset (before age 65) (Lindsay et al., 2002; Vieira et al., 2013; Peters et al., 2015), poor health conditions, and psychosis symptoms presence (Mortimer et al., 1992; Lyketsos et al., 2002; Peters et al., 2015). Table 2.1 is a summary of the past studies on risk factors for dementia and dementia progression.

Some other factors were also examined in several studies, but still need more evidence on the effect of dementia progression rate, such as Vitamin supplement (Kang et al., 2008), depression (Andersen et al., 2005), exercise habits (Larson et al., 2006; Scarmeas et al.,2009), leisure activity (Stern, 1999, 2012), and diet (Morris al.,2003; Feart et al., 2009; Scarmeas et al.,2009). Depression was reported to have an interaction effect with gender (Dal et al., 2005). It should be noted that Apolipoprotein epsilon 4 (APOE ε4) is the largest known genetic risk factor for late-onset Alzheimer's disease (Farrer et al., 1997; Kleiman et al., 2006; Wilkosz et al., 2010; Tschanz et al., 2011; Sadigh-Eteghad, Talebi & Farhoudi, 2012; Sadigh-Eteghad et al., 2015). However, there are different opinions about the influence of APOE ε4 on the rate of cognitive decline. It is reported that APOE ε4 does not significantly influence the rate of disease

progression in cognitive or functional domains (Kleiman et al., 2006). According to Cosentino et al., (2008) and Elias-Sonnenschein (2011), APOE ε4 may influence rate of cognitive decline most significantly in the earliest stages of Alzheimer disease. Sweet et al., (2012) found that APOE ε4 alleles were associated with reduced age at midpoint of cognitive decline and psychosis was associated with an increased rate of cognitive decline. Factors such as exercise habits, leisure activity, and diet are difficult to assess and have no standard in comparative studies.

Table 2.1

Selected literature on risk factors for dementia/dementia progression

Factors	**Studies included the factor on the left for dementia progression**
Risk factors discussed for both incident of dementia and progression rate	
Education	Shadlen 2005; Caamano-Isorna et al., 2006; Li et al., 2014; Peters et al., 2015;
Gender	Yu & Ghosh, 2010; Tschanz et al., 2011; Li et al., 2014; Peters et al., 2015
Age at onset	Lindsay et al., 2002; Peters et al., 2015
Vascular health conditions	Larson et al., 2005; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005; Crane et al., 2013; Peters et al., 2015; Baumgart et al., 2015
Neuropsychological symptoms	Mortimer et al., 1992; Lyketsos et al., 2002; Sweet et al., 2012; Peters et al., 2015
APOE ε4	Kleiman et al., 2006; Cosentino et al., 2008; Elias-Sonnenschein et al., 2011
Risk factors discussed for incident of dementia only	
Vitamin supplement	Kang et al., 2008; Masaki et al., 2000
Smoking	Anstey et al., 2007
Depression	Andersen et al., 2005; Korczyn and Halperin, 2009
Exercise habits	Larson et al., 2006; Scarmeas et al., 2009
Leisure activity	Stern, 1999; Stern, 2012
Diet	Morris et al.,2003; Feart et al., 2009; Scarmeas et al., 2009

2.2. Trajectory of Cognitive Decline and Functional Decline in People with Cognitive Impairment

Cognitive decline may not be linear and cognitive trajectories may differ from one cognitive domain to another (Cloutier et al., 2015). Years of stable performance followed by a rapid decline just prior to diagnosis was observed for delayed recall, working memory, and spatial memory. In contrast, a gradual linear decline was observed for immediate recall, executive function, and visual-spatial abilities. Mortimer et al., (1992) found lower scores on the verbal neuropsychological tests at the time of study entry, more aggressive behavior, and sleep disturbance at entry time predicts faster cognitive decline.

Functional decline is associated with cognitive decline but follows a different course (Mortimer et al., 1992). These two domains must be assessed separately, because they are two distinct aspects in dementia severity (Bruce et al., 1989). Paranoid behavior, hallucinations, activity disturbances during the first year, the presence of extrapyramidal signs, and lower scores on nonverbal neuropsychological tests at the time of entry into the study predicted faster functional progression (Bruce et al., 1989). Hallucinations occurred independent of cognitive severity and may identify a distinct subgroup of patients with a rapid functional progression.

Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) are often used as an older person's functional assessment in senior care. ADL typically refers to activities involving functional mobility (walking, wheelchair mobility, and transfers) and personal care (feeding, hygiene, toileting, bathing, and dressing). IADL as defined by Katz (1983), involves shopping, cooking, housekeeping, laundry, use of transportation, managing money, managing medication, and the use of the telephone. IADL is concerned with a person’s ability to cope with her/his environment in terms of adaptive tasks (Katz, 1983). A study in Japan

showed that deterioration in ADL is more significant than in IADL, suggesting that factors such as motivation or perceptual, sensory, and motor abilities could be important in IADL performance (Sauvaget et al., 2002). Dodge et al. (2006) found that the level of cognitive decline can predict the decline in performing IADL.

Mini Mental Status Examination (MMSE) is a 30-point questionnaire that is used commonly in clinical practice to measure cognitive impairment. Brown et al., (2014) showed that MMSE scores and functional performance scores were not significantly associated with one another. Reed et al. (1989) found that MMSE score explained only about one-third of the variance in both instrumental ADLs and physical ADLs in the whole sample. In the less demented samples, the MMSE and ADLs were independent of one another in half of the samples.

The CDR score is an important predictor for overall performance (Luana, 2013). CDR was developed to evaluate the severity of dementia for the Memory and Aging Project at Washington University School of Medicine in 1979. It can be used to stage dementia. It is a four-point scale in which CDR-0 connotes no cognitive impairment and CDR-3 is the most severe stage of dementia. In assigning a Global CDR, six domains are scored independently and added together to construct the overall CDR table. The six domains are memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The impairment index was found to be significantly varied among different diagnosis groups (Mitnitski et al., 1999). Brown et al. (2014) also stated that no significant differences between the culturally and linguistically diverse groups were obtained.

Several studies assume that there is a cognitive reserve mechanism against the manifestation of the pathological changes of dementia. The mechanism could be triggered by

factors such as educational or occupational attainment. Cognitive reserve (CR) is the ability of an individual to cope with advancing brain pathology so that this individual remains free of symptomatology. In the study of Scarmeas et al. (2003), epidemiological evidence and in vivo neuro-metabolic data suggest that CR may be mediated through education or IQ. This study investigated differential brain activation in 17 healthy young adults and 19 healthy elders. Using non quantitative PET scanning, the authors assessed relative regional cerebral blood flow while subjects performed a serial recognition memory. Actually, there were evidence provided that cognitive reserve could lead to interventions to slow cognitive decline or reduce the risk of dementia (Stern, 1994; Letenneur et al., 1994; Evans et al., 1993; Stern et al., 1995). Furthermore, leisure activities later in life can increase CR (Stern, 1999; Stern, 2012).

Compensation mechanism is discussed in several studies. In the study by Clément & Belleville (2010), functional neuroimaging was used to test the effect of disease severity on the brain activation of people at risk for Alzheimer's disease. It was found that in MCI patients higher-cognition activity activated additional regions in the right ventrolateral and dorsolateral prefrontal brain areas, relative to control subjects. Additional areas of hyper activation were found in the right prefrontal area. In MCI patients, lower-cognition activities showed decreased activation in posterior areas. Furthermore, imaging studies have suggested that given comparable clinical severity of dementia, Alzheimer’s disease pathology is more advanced in patients with higher educational and occupational attainment (Stern et al., 1995).

Reversion from MCI was common in a cohort of patients seen at dementia research centers. Nonetheless, those who reverted remained at increased risk for future cognitive decline (Koepsell & Monsell, 2012). Those with impairment in more than one cognitive domain were

more likely to progress or remain impaired than those with single-domain impairment (Manly et al., 2008).

2.3. Research Methods for Modeling Trajectory for Longitudinal Data

Longitudinal studies collect repetitive measurements on the same subject over a period of time. A trajectory describes the course of change in a variable over time. Researchers often are interested not only in the trajectory of variables over time, but also in how covariates may affect their shape. Hierarchical modeling (Goldstein, 1995) and latent curve analysis (Meredith & Tisak 1990; Muthen, 1989; Willett & Sayer, 1994) were used to measure these relationships. These two methods estimate the population average trajectory and use covariates to explain variability about this average (Jones et al., 2001).

Nagin (1999) proposed group-based modeling approach assuming that the population is composed of distinct groups, each with a different underlying trajectory. Based on the model coefficient estimates, for each individual *i* the probability of membership in group *j* is calculated on the basis of the individual's longitudinal pattern of behavior, Y_i. The estimated probability of membership in group *j* with pattern Y_i is denoted by $\hat{P}(j|y_i)$. It is computed as follows:

$$\hat{P}(j|Y_i) = \frac{\hat{P}(Y_i|j)\hat{\pi}_j}{\sum_j \hat{P}(Y_i|j)\hat{\pi}_j} \quad (2.\ 1)$$

$\hat{\pi}_j$ is the proportion of population composing group *j*. $\hat{P}(Y_i|j)$ is the estimated probability of having the pattern Y_i given belonging to group *j*.

Leffondré (2004) proposed 24 statistical measures to capture the nonlinear patterns or shapes of change over time for delirium severity and also identified distinct trajectory types. Chaves et al., (2010) used survival analysis models and found that vascular risk factors and education were strong predictors of decline. A mixture survival model was used by Yu and Ghosh (2010) to estimate dementia onset and death jointly. The model considered the effect of

competing risks, which are defined as dementia and dementia-free death. Also, the Markov chain Monte Carlo method was used for parameter estimation. Wei et al. (2014) evaluated the effect of death as a competing event to the development of dementia in a longitudinal study of the cognitive status of elderly subjects. The study used a multi-state Markov model with three transient states: intact cognition, mild cognitive impairment, and global impairment and dementia as one absorbing state transitions.

Mixture models are useful for modeling unobserved heterogeneity in a population. Zhao et al. (2015) presented a mixture of the Gaussian processes model to predict the disease progression course in multiple sclerosis (MS) patients and disability levels in early Parkinson's patients. An appropriate parametric model f (y, λ) is assumed for the phenomenon to be studied. Y= (y_1, y_2, …y_T) denotes the longitudinal sequence of an individual's behavioral measurements over the T periods of the measurement. There are unobserved subpopulations differing in their parameter values. In this case, the marginal density for the data ***y*** can be written as:

$$\sum_{k=1}^{K} P_r(C = k) P_r\,(Y = \mathbf{y} | C = k) = \sum_{k=1}^{K} p_k f(\mathbf{y}, \lambda_k) \qquad (2.\ 2)$$

where $P_r(C = k)$ is the probability of belonging to class *k*, *k=1…K,* and it is denoted as p_k. $f(\mathbf{y}, \lambda_k)$ is the probability showing the sequence **y** given class *k.*

Mixed effect models permit inference regarding the average response trajectory over time. The trajectory varies with each individual subject characteristic such as demographic or other treatment factors. Traditional regression methods assume that all observations are independent. For longitudinal studies, correlations between observations need to be considered and addressed. There are two main approaches to deal with a correlation. A full model includes specific assumptions regarding the correlation of outcomes within subject. General regression methods can be used and the standard errors can be corrected to account for the correlated

outcomes. Another approach for dealing with longitudinal data is known as generalized estimating equations (GEE). There are several assumptions in GEE models: 1. the responses are correlated or clustered instead of independent, 2. variance are either homogenous or heterogeneous, and 3. errors are correlated.

Modeling longitudinal data using mixed effect models and other techniques has become increasingly popular. The models allow the change in the outcome measurement can be associated with the change in the exposure condition. Often it is the case that repeated measures are correlated within subjects and thus require special statistical techniques for analysis and inference. The models are used to characterize any growth or process, to assess the effect of risk factors on human health, and to evaluate the effectiveness of treatments. It plays a key role in investigating systematic change, growth, and inter-individual variability in epidemiology, clinical research, and behavioral studies.

CHAPTER 3. PROPOSED TRAJECTORY MODELS

3.1. Trajectory Models

Longitudinal studies have long played a critically important role in biological and social sciences, such as developmental psychology, behavioral science, and empirical clinical studies. Modeling for the trajectory of a longitudinal data can be referred to as growth curve models or trajectory models. These models include repetitive measurements for the same subject along with time.

The hidden mechanism of dementia pathology is very complex and the manifestation of individual performance in daily life is highly variable. Therefore, choosing the correct modeling tool can be difficult. Regression model is a common statistical method to mathematically describe the relationship between some predictors and the response variable.

There are several steps in finding the correct modeling tool. The step in finding the correct modeling tool is to explore the data by performing univariate analysis on interested factors. The purpose of data exploring is to describe and summarize the data, and furthermore, identify the potential patterns in the data. The statistics that can be used to describe patterns in univariate analysis include mean, mode and median (central tendency) and range, variance, maximum, minimum, quartiles, and standard deviation (dispersion). The second step is to examine correlation for all the possible predictor variables. The purpose of correlation analysis is to quantify the association between two variables. However, non-linear association between two variables cannot be detected by correlation analysis. Graphical illustration is also useful to explore associations between variables. Third, select variables that would enter model building. This is completed to ensure that the model explains the data in the simplest way and not missing important predictors. The correlation analysis would identify any collinearity in the data to avoid

redundant predictors. The fourth step is to fit the proposed model using existing data and find the goodness of fit using model evaluation criteria. The final step is to cross validate the model to make sure the model can be generalized to an independent data set. Common types of cross validation used are boot-strap and k-fold cross validation.

The primary goal in this study is to investigate how time typically affects CDR SUM score and also include some important variables in the model. The analysts seek to eliminate the unrelated variables and include only those with a true relationship. In this dissertation, six strategies are considered to model the relationship between CDR SUM score and relevant features of a cognitive decline patient. Linear regression model is the first and simplest method. Mixed effect model provides an alternative representation of the change trajectories modeled via polynomial models (e.g., quadratic, cubic, etc.) and is particularly useful for representing complex shaped trajectories in a parsimonious manner. The fourth strategy of hierarchical modeling captures the growth curves, which is the individual variation in developmental trajectories using a random coefficients modeling strategy. Hierarchical modeling has great flexibility in characterizing nonlinear patterns or shapes of change over time. Semiparametric models with and without correlation are the last two strategies proposed in this study.

3.1.1. Strategy One: Linear Model for Each Individual

For each subject, a simple regression model can be fitted to simulate the observed CDR SUM score change along with time. Assumption is made that for each particular combination of time-constant variables and time-varying variables, the intercept is different. More precisely, CDR SUM score is regressed on time individually for each participant. This new model assumes that each subject has an individual slope of CDR SUM score as the change rate, and the other features of the patient determines the intercept of the model. The model takes the form of

$$y_{ij} = \beta_0 + \beta_{1i} t_{ij} + \sum_{q=1}^{c} \theta_k \, x_{iq} + \sum_{l=1}^{d} \mu_l \, z_{ijl} + \epsilon_{ij}$$

$$\beta_{1i} \sim N(0, \sigma_{\beta_1}^2)$$

$$\epsilon_{ij} \sim N(0, \sigma_{\varepsilon}^2) \qquad (3.\ 1)$$

where β_0 is the fixed intercept and β_{1i} are random individual slopes of the *i*th subject. t_{ij} are the durations since onset of cognitive decline for subject *i* at time *j*. X_{iq} is a *c* dimension time-constant covariant matrix for subject *i* at all times, for example gender of subject *i*, the years of education for subject *i*, and so on. Z_{ijl} is a *d* dimension time-varying covariant matrix for subject *i* at time *j*. z_{ijl} includes all the changing features of subject *i* at time *j*, such as health condition, drug usage, living conditions, life style change, presence of neuropsychiatric symptoms, etc. The slope β_{1i} and error term ϵ_{ij} are assumed to follow normal distribution, with consistent variance $\sigma_{\beta_1}^2$ and σ_{ε}^2 respectively. The selection of the explanatory variables x_{iq} and z_{ijl} will be discussed in the next chapter.

The advantage of this strategy is its simplicity. Each subject has a unique model with an individual intercept and slope. However, this strategy does not give too much information on the overall pattern. Although the intercepts and slopes can be extracted to have another statistical analysis, due to variability of individual demographic and medical profiles, it is not clear how these factors would affect the dependent variable generally. The slopes and error terms may not follow normal distribution as it was arbitrarily assumed. Furthermore, the number of parameters increase with the number of subjects, plus each model has five standard errors for each term in the model.

3.1.2. Strategy Two: Polynomial Regression Model

The relationship between CDR SUM score and time may not be a straight line. Although fluctuations are a core feature of dementia with Lewy bodies, dementia is progressive (inducing a gradual functional decline), degenerative (getting worse over time), and irreversible. Polynomial regression model is an efficient tool to present nonlinear growth curve by modeling how variables drive responses and the direction of responses. The polynomial regression model can be denoted as

$$y_{ij} = \beta_0 + \sum_{p=1}^{P} \beta_{pi} t_{ij}^{p} + \sum_{q=1}^{c} \theta_k \, x_{iq} + \sum_{l=1}^{d} \mu_l \, z_{ijl} + \epsilon_{ij}$$

$$\beta_{pi} \sim N(0, \sigma_{\beta_p}^2)$$

$$\epsilon_{ij} \sim N(0, \sigma_{\varepsilon}^2) \qquad (3.\ 2)$$

where β_0 is the fixed intercept and and β_{pi} are random individual slopes for the polynomial term t_{ij}^{p} of the i^{th} subject. X_{iq} is a *c* dimension time-constant covariant matrix for subject *i* at all times, such as gender of subject *i* and the years of education for subject *i*. *P* is the degree of the polynomial function. Z_{ijl} is a d dimension time-varying covariant matrix for subject *i* at time *j*. Z_{ijl} includes all the changing features of subject *i* at time *j*. The slope $\beta_{\mathrm{p}i}$ and error term ϵ_{ij} are assumed to follow normal distribution, with consistent variance $\sigma_{\beta_{\mathrm{p}}}^2$ and σ_{ε}^2, respectively.

This strategy of using polynomial terms would help to capture the subtle change of the CDR SUM score along with time. However, polynomial regressions fit optimally only when it is the exact nature of the true relationship. Splines is another option to simulate the shapes of curves.

3.1.3. Strategy Three: Nonlinear Model with Time Series Correlation

In the previous two models, the response variable is independent with each other for the same subject. However, in many cases in longitudinal studies, there is possibility that subjects with higher baseline scores may, on average, be more strongly affected by time. In other words, there is possible systematic within-subject correlation among the random effect for the intercept and the random effect for the slope. We represent this correlation effect by defining an exponential correlation function in the term $\epsilon_i(t_{ij})$ in Equation 3.3:

$$y_{ij} = \beta_0 + \sum_{p=1}^{P} \beta_{pi} t_{ij}^{p} + \sum_{q=1}^{c} \theta_k \, x_{iq} + \sum_{l=1}^{d} \mu_l \, z_{ijl} + \epsilon_i(t_{ij}) \tag{3. 3}$$

In this model, the term $\epsilon_i(t_{ij})$ represents the within-patient variation, comprising of an exponential correlation function $\delta_i(t_{ij})$ and measurement error ω_{ij}:

$$\epsilon_i(t_{ij}) = \delta_i(t_{ij}) + \omega_{ij} \tag{3. 4}$$

where ω_{ij} is the residual component , and ω_{ij}~N$(0, \sigma_{\omega}^2)$. The distribution of $\delta_i(t_{ij})$ follows a multivariate normal density with mean 0 and variance-covariance matrix $\sum$:

$$\delta_i(t_{ij}) \sim MVN\,(0, \sum) \tag{3. 5}$$

$\delta_i(t_{ij})$ follows exponential correlation function $\rho(t)$:

$$\rho(t) = Corr\,(\delta_i(t_0), \delta_i(t + t_0)) = e^{(-\frac{|t|}{\tau})} \tag{3. 6}$$

τ is the rate of decay for the correlation function for time between observations of $|t|$. $\rho(t)$ allows correlation between observations decay along with time. Therefore, observations farther apart in time are less correlated.

3.1.4. Strategy Four: Multilevel Quadratic Model

Multilevel modeling (also known as hierarchical linear models, nested data models) recognizes data has hierarchical structures that allow each level with residual components.

Before modeling a relationship between a response variable and some of the covariates that are observed along with the response, data structure must be understood. The structure of data can be viewed as hierarchical, and the observation is the result of effects in several levels. Multilevel modeling uses regression methods and allows variables to have multiple levels that have a zero-mean variance. In this study, time is regarded as the first level effect, and other time-related effects (including time-constant and time-varying effects) are the second level effects. Figure 3.1 shows the two-level model structure in this study.

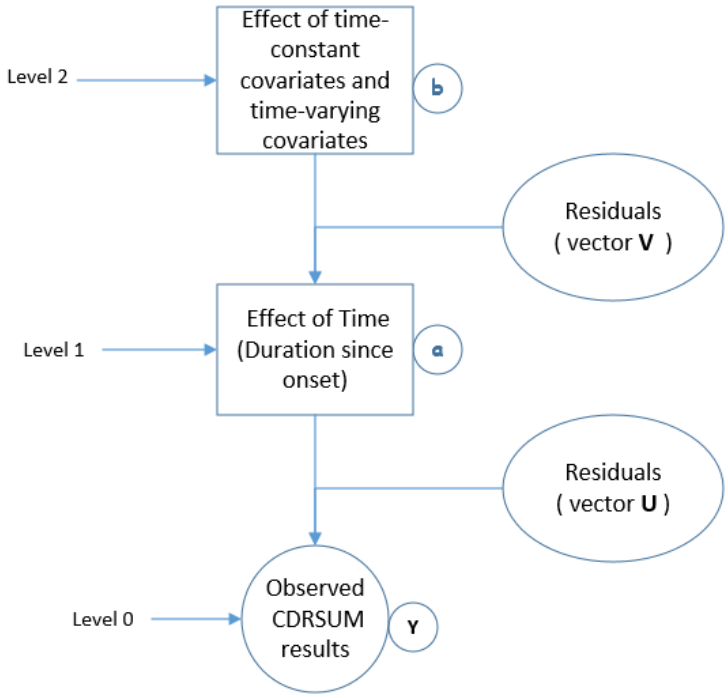

Figure 3.1. Two-level model structure

This research assumes that the observations Y are explained by the effect ***a*** (duration of time since onset) and a normally distributed residual (denoted as U). Likewise, the effect ***a*** in turn is explained by a superordinate effect ***b*** (time-constant and time-varying covariates) and a normally distributed residual (denoted as V). Linearity assumption is not good enough to capture the change of the trajectory curves. Tests are performed for polynomial models with quadratic

and cubic terms respectively, and it is found that the slope of cubic term is zero and can be discarded. Therefore, quadratic curve is selected for model building. The model can be expressed as

Level 0

$$y_{ij} = \beta_0 + \beta_{1jr} t_{ijr} + \beta_{2jr} t_{ijr}^2 + \epsilon_i(t_{ijr}) \quad (3.\ 7)$$

Level 1

$$\beta_{1jr} = a_{10r} + U_{1jr} \quad (3.\ 8)$$
$$\beta_{2jr} = a_{20r} + U_{2jr}$$

Level 2

$$a_{10r} = b_{100} + b_{101} * tx + V_{0r} \quad (3.\ 9)$$
$$a_{20r} = b_{200} + b_{201} * tx + V_{1r}$$

With

$$\begin{pmatrix} U_{1jr} \\ U_{2jr} \end{pmatrix} \sim \mathrm{N} \begin{pmatrix} 0 & \gamma_{00}^2 & \gamma_{01} \\ 0' & \gamma_{01} & \gamma_{10}^2 \end{pmatrix}$$

$$tx = \sum_{q=1}^{c} \theta_k \, x_{iq} + \sum_{l=1}^{d} \mu_k \, z_{ijl} \quad (3.\ 10)$$

With

$$\begin{pmatrix} V_{0r} \\ V_{1r} \end{pmatrix} \sim \mathrm{N} \begin{pmatrix} 0 & \varphi_{00}^2 & \varphi_{01} \\ 0' & \varphi_{01} & \varphi_{10}^2 \end{pmatrix}$$

In Level 0, y_{ij} is the observed CDR SUM score for subject *i* at time *j*. β_0 is the fixed intercept and β_{1j} are random individual slope of the j^{th} subject. *r* specifies the particular state for both time-constant and time-varying covariates for subject *i* at time *j*. t_{ijr} are the durations since

onset of cognitive decline for subject *i* at time *j*. *r* specifies the particular state for both time-constant and time-varying covariates for subject *i* at time *j*.

In Level 1, the slope of linear term t_{ijr} and quadratic term t_{ijr}^2 are divided into two parts: *a* and *U* (effect of time and residuals). In Level 2, X_{iq} is a *c*-dimension time-constant covariates matrix for subject *i*. Gender, level of education for subject *i* and age at onset are selected in X_{iq} in this study. $Z_{ijl}$is a *d*-dimension time-varying covariate matrix for subject *i* at time *j*. It includes all the changing features of subject *i* at time *j*.

This multilevel model structure incorporates the factors in a manner that accounts for errors at each level. It also determines the impacts of Level 1 factors and Level 2 factors based on individual observations. Furthermore, the structure controls the specification of the covariance matrix for the residuals.

3.1.5. Strategy Five: Semiparametric Mixed Effect Model without Correlation

Semiparametric modeling methods are increasingly used for capturing subtle changes in longitudinal data. In many regression models, normality assumption is needed. However, in semiparametric mixed effect models, ordinal variables even in small sample sizes can fit in nonparametric models. Additionally, normality assumption is not required for semiparametric mixed models.

In the semiparametric mixed effect model of this study, the average effect of time is represented by a penalized smoothing spline. The response variable y_{ij} is assumed to depend on the combination of an average effect of time and other covariates, as shown in Equation 3.11. The effect of time and other covariates on CDR SUM score (the response) is complicated. Nonlinearity itself cannot fully explain the heterogeneous shape of trajectories. Therefore,

penalized spline and its mixed model representation is a good solution to feature individual profiles.

$$y_{ij} = f(t) + \sum_{q=1}^{c} \theta_k \, x_{iq} \; + \sum_{l=1}^{d} \mu_k \, z_{ijl} \; + \; \epsilon_i(t_{ijr}) \tag{3. 11}$$

$$\epsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$$

$f(t)$ is a panelized spline smooth function which reflects the overall trend of CDR SUM score along with time.

$$f(t) = \beta_0 + \beta_{1jr} t_{\,ijr} + \beta_{2jr} t_{ijr}^2 + \sum_{k=1}^{K} u_k (t_{\,ijr} - \mathrm{K}_k)_+^2 \tag{3. 12}$$

$$0 < \mathrm{K}_1 < \; \mathrm{K}_2 < \cdots < \; \mathrm{K}_K < \max(\boldsymbol{t_{ijr}}) \tag{3. 13}$$

The number of knots *K* is fixed and large enough to ensure the flexibility of the curve. $\mathrm{K}_{\boldsymbol{1}} \ldots, \mathrm{K}_{\boldsymbol{k}}$ are a set of distinct fixed knots ranging from 0 to $\max(\boldsymbol{t_{ijr}})$. The knots are chosen as quantiles of $t_{\,ijr}$ with probabilities 1/(K+1), … ,K/(K+1). The method to select the number of knots and the codes associated with selection is documented in Ruppert (2002) and Durbán et al., (2005). We use truncated lines as the basis for regression. In Equation 3.12, u_k refers to the weight of each linear function and $(t_{ijr} - \mathrm{K}_k)_+$ refers to the the *k*th linear function with a knot at K_k.

$$(t_{ijr} - \mathrm{K}_k)_+ = \begin{cases} t_{\,ijr} - \mathrm{K}_k \; : \; if \; t_{\,ijr} - \mathrm{K}_k > 0 \\ 0 \qquad\quad : \; if \; t_{\,ijr} - \mathrm{K}_k \geq 0 \end{cases} \tag{3. 14}$$

.

Referring back to the regression model, the basis of the spline model for $\boldsymbol{f(t)}$ is

$$[1 \;\; t_{\,ijr} \;\; t_{\,ijr}{}^2 \;\; (t_{\,ijr} - \mathrm{K}_1)_+ \;\; \ldots (t_{\,ijr} - \mathrm{K}_k)_+ \;\; (t_{\,ijr} - \mathrm{K}_1)_+{}^2 \ldots (t_{\,ijr} - \mathrm{K}_k)_+{}^2 \;] \tag{3. 15}$$

3.1.6. Strategy Six: Semiparametric Mixed Effect Model with Correlation

In semiparametric mixed effect models, there is a possible systematic correlation within subject. In other words, we assume the outcome variable has more correlation if the observations are closer in time collected. The most common way to express the correlation is through the random effect for the intercept and the random effect for the slope. We allow this correlation effect by defining an exponential correlation function in the term $\epsilon_i(t_{ij})$ in Equation 3.16.

$$y_{ij} = f(t) + \sum_{q=1}^{c} \theta_k \, x_{iq} \; + \sum_{l=1}^{d} \mu_k \, z_{ijl} \; + \; \epsilon_i(t_{ijr}) \tag{3. 16}$$

In this model, the term $\epsilon_i(t_{ij})$ represents the within-patient variation, comprising of an exponential correlation function $\delta_i(t_{ij})$ and measurement error ω_{ij}:

$$\epsilon_i(t_{ij}) = \delta_i(t_{ij}) + \omega_{ij} \tag{3. 17}$$

where ω_{ij} is the residual component , and $\omega_{ij} \sim \mathrm{N}(0, \sigma_{\omega}^2)$. The distribution of $\delta_i(t_{ij})$ follows a multivariate normal density with mean 0 and variance-covariance matrix $\sum$:

$$\delta_i(t_{ij}) \sim MVN\,(0, \sum) \tag{3. 18}$$

Also $\delta_i(t_{ij})$ follows exponential correlation function $\rho(t)$:

$$\rho(t) = Corr\,(\delta_i(t_0), \delta_i(t + t_0)) = e^{\left(-\frac{|t|}{\tau}\right)} \tag{3. 19}$$

where τ is the rate of decay for the correlation function for time between observations of $|t|$. Therefore, observations farther apart in time are less correlated.

3.2. Model Evaluation Methods

It is important to remember that the models are just an approximation to the reality of the true relationship among variables. The noise factors, unpredictable environment and complex systematic operation in human bodies make it impossible to predict the exact outcomes of any prediction model. However, even if the predictions are not exactly the same as the observation

results, we can still find a best way to describe or predict the outcome variables. In model selection, we have several models to find the best approximation that can provide an adequate description of the data. In this study, we used a unique combination of model selection criteria, including Akaike Information Criterion (AIC), Bayesian information criterion (BIC), R-squared and correlation coefficient.

AIC and BIC are both penalized-likelihood criteria. They are used for choosing best predictor subsets in regression and often used for comparing non-nested models (Cherkassky & Mulier, 2007). AIC is an estimate of a distance between the unknown true likelihood function of the data and the fitted likelihood function of the model. Therefore, the lower the AIC, the better a model is considered to be closer to the true observed results. AIC is defined as:

$$AIC = -2L_m + 2m \tag{3. 20}$$

where L_m is the maximized log-likelihood of the model and m is the number of parameters in the model. BIC (also called the Schwarz Criterion) is an index used as an aid in choosing between competing models. It is defined as

$$BIC = -2L_m + m * \ln n \tag{3. 21}$$

where n is the sample size, L_m is the maximized log-likelihood of the model and m is the number of parameters in the model. The index takes into account both the statistical goodness of fit and the number of parameters that have to be estimated to achieve this particular degree of fit, by imposing a penalty for increasing the number of parameters. BIC is an estimate of a function of the posterior probability of a model being true. Therefore, a lower BIC means that a model is considered to be more likely to be the true model. Both criteria are based on various assumptions and asymptotic approximations. Comparisons of AIC or BIC cannot be given a statistical interpretation. Kass and Raftery (1995) categorized differences in BIC between models of >10 as

"very strong" evidence in favor of the model with the lower BIC; 6–10 as "strong" evidence; 2–6 as "positive" evidence; and 0–2 as "weak" evidence. In practice, a drop in AIC or BIC of 2 is often a threshold for considering one model over another. Welch (2006) stated that BIC and AIC performed poorly because they consistently selected models that were too small (*i.e.*, contained many fewer parameters than the true model). We used other selection criteria in conjunction with AIC and BIC in model selection (Burnham & Anderson, 2002).

In order to examine the goodness of fit for the mixed models, R-squared (R^2, also known as coefficient of determination) was used as the first measurement of model goodness of fit statistic. R-squared is widely used for linear regression model for examining how well the model fits the data. However, R-squared is only appropriate in linear regression model. Therefore, the linear model of fitted and observed values as shown in Equation 3.22 was made and then the R-squared in Equation 3.23 was evaluated for this linear model. R-squared measures the proportion of the observed value variation that is explained by the linear model. The second measurement is the correlation in Equation 3.24 between the fitted and the observed values. The higher the correlation, the better the fitted values from a certain model simulate the observed value.

$$\hat{y}_k = a^* (y_k) + b \tag{3. 22}$$

$$R^2 = 1 - \frac{\sum (y_k - \hat{y}_k)^2}{\sum (y_k - \bar{y})^2} \tag{3. 23}$$

$$r = \frac{n(\sum y_k \hat{y}_k) - (\sum y_k)(\sum \hat{y}_k)}{\sqrt{[n\sum {y_k}^2 - (\sum y_k)^2]\left[n\sum {\hat{y}_k}^2 - (\sum \hat{y}_k)^2\right]}} \tag{3. 24}$$

In equations 3.22, 3.23 and 3.24, y_k is the *k*th observed value, $\hat{y}_k$ is the *k*th predicted value, and $\bar{y}$ is the grand mean. Both R-squared and correlation coefficient r are simple to compute and interpretable for the conformity between observed outcomes and predicted outcomes.

CHAPTER 4. TRAJECTORY MODELING OF COGNITIVE DECLINE

In this chapter, we evaluate the performance of the six models developed in Chapter 3. The data used to evaluate and compare the performance of the six models were extracted from the National Alzheimer's Coordination Center (NACC) Uniform Data Set (UDS) database. The database provided comprehensive records of demographic and clinical information on recruited patients since September 2005. These patients made follow-up visits to the center through September 2015 or made contact with the center annually until they were deceased or dropped out.

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 (ADCs) supported by the U.S National Institute on Aging. NACC UDS is a cumulative database including clinical evaluations, neuropathology data from 2005 to the present. The UDS is the primary data set used by researchers interested in clinical data. The NIA/NIH Alzheimer's Disease Centers (ADCs) began submitting UDS data to NACC in September 2005, using the UDS Forms to collect standardized clinical data from subjects who are evaluated on an approximately annual basis. Since 2005, the UDS forms have undergone two major revisions to reflect advances in the science and incorporate new diagnostic criteria. The patients are recruited from the clinics, and all enrolled patients undergo a standardized and longitudinal evaluation. The clinic-based population includes subjects with Alzheimer's disease and related disorders, as well as cognitively normal subjects and those with mild cognitive impairment (MCI). We divided the data into two parts: training data and test data. The training data are separated for learning and finding the potential relationships between variables. The training data is used to fit

the parameters of the models. The test data are used only to assess the performance of the proposed models.

Figure 4.1 is a grid plot of the CDR SUM score versus time since onset in years by subject. The 56 Patients in the plot are randomly selected from NACC UDS database (Sep 2005-Sep 2015). Each patient's data are shown in a separate panel in different color circles, along with simple linear regression line fit to the data in that panel. The plot shows the variability in times of visit, patient entry time, and trend along with time individually.

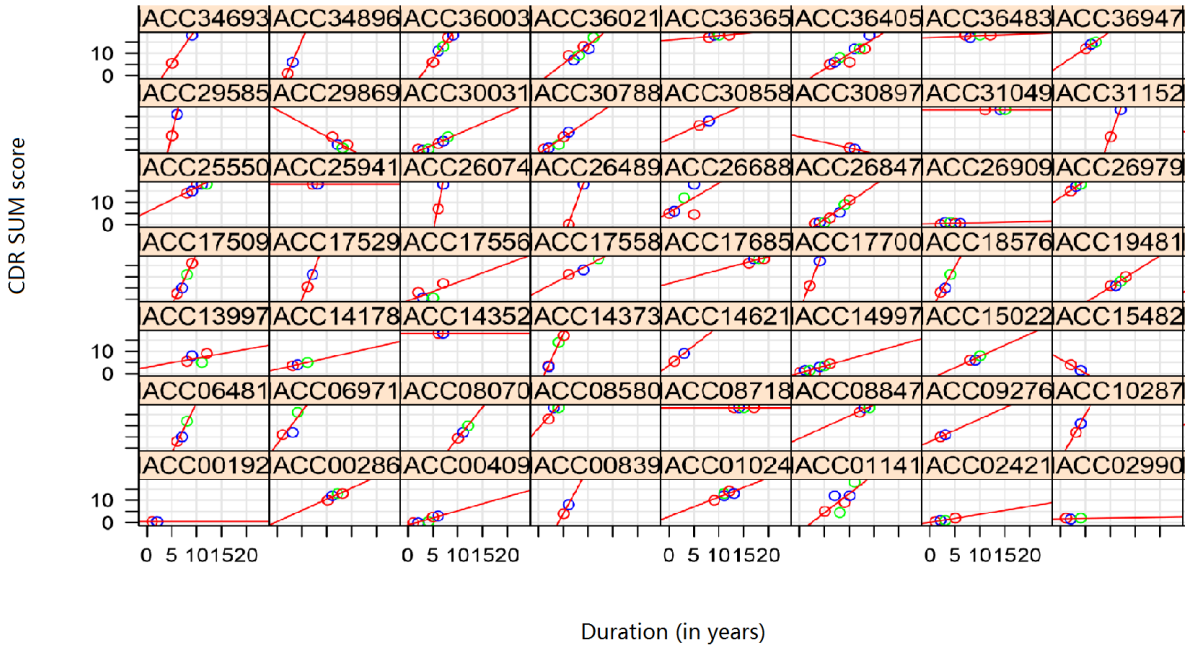

Figure 4.1. Panel Plot of 56 patients' trajectory of CDR SUM score
Each panel is the illustration of duration and CDR SUM score. Horizontal axis is the duration since onset, and vertical axis is the CDR SUM score.

In the following sections, we will first summarize the data structure, and then conduct exploratory data analysis to describe the relationships among variables. The training data is used to fit the six models proposed in the previous chapter. The unique model selection criteria will be

applied to evaluate goodness of fit and then select the best model for prediction. The last two semiparametric mixed effect models are selected and used for testing model robustness.

4. 1. Training Data

The training data are the data for learning and describing the potential relationships between objective variable and other predictive variables. It is used to fit the parameters of the models. The patients deceased by the time of data acquisition were selected as training data for model building. Patients who made less than two visits were excluded. Those who had missing or unknown values in any predictive variables were also excluded. 2,669 patients and 9,615 records were left in the training data set after the exclusion criteria was applied, as is shown in Figure 4.2.

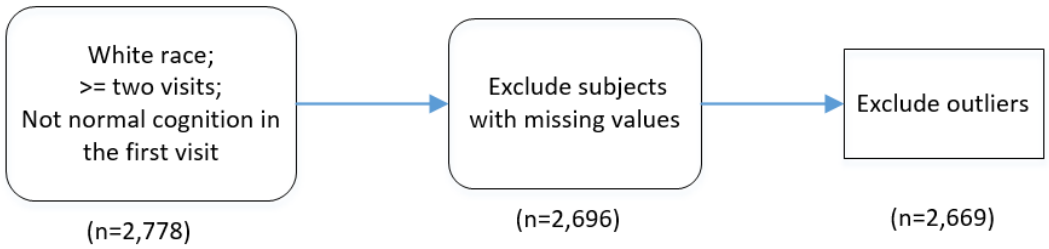

Figure 4.2. Flowchart of patient selection procedure

Records for patients who made only one visit are discarded due to two considerations. First, the cause of dementia and other causes of death are competing factors, and there is ambiguous information in the data for the cause of death. Second, one record for a patient does not provide information on the trend of cognitive decline.

4.1.1. Variables selected to include in models

The aim of variable selection is to construct a model that explains well the relationships in the data. Stepwise methods use hypothesis testing based methods for choosing between

models (Bursac, Gauss, Williams, & Hosmer, 2008). Criterion-based methods compare models in a wide searching manner.

Time is a primary factor to be studied in dementia progression. Other covariance includes time-constant and time-varying variables. Age at onset refers to the age at which dementia symptoms began, not the age at which the diagnosis was made. Age at onset was identified through the clinical history, preferably given by a knowledgeable caregiver or family member. Memory decline accompanied by symptoms that reflect significant functional change in the individual's abilities (e.g., in judgment, personal finances, home activities, orientation). The observed changes must be significant enough to arouse caregiver concern over safety to determine age at onset of dementia symptoms. The questions that probe for functional change may include the following: 1. when did the individual manifest constant forgetfulness, resulting in an inability to manage his/her daily schedule? 2. When did the individual display a significant failure in judgment in responding to solicitations or subscriptions? 3. When did the individual manifest a significant change in cooking abilities or other home activities?

It is commonly recognized that age is the most obvious risk factor for cognitive decline. Holland (2012) found that rates of decline in Alzheimer's disease decrease with age. We use scatter plot to illustrate the relationship between CDR SUM score and age (Figure 4.3). No typical pattern shows that higher CDR SUM score is associated with older age. We also did linear regression to explore the quantitative relationship between CDR SUM score and age. The linear model can only explain 2% of the variance in the linear model. Among the factors that related to time (age at onset, duration, and age), we can see that age is the sum of Age at onset and DURATION. If we include all these three factors in the model, their values will be highly correlated and then collinearity will occur. Collinearity tends to inflate the variance of at least

one estimated regression coefficient. Due to parsimonious selection of variables, simplicity and clarity of model building, we have to avoid collinearity. Since the goal of this study is to explore the typical trajectory of CDR SUM score along with time, we would adopt the method in Bernick et al. (2012) to consider baseline age (Age at onset) as one of the variables to predict CDR SUM. Furthermore, we include duration to consummate the effect of time.

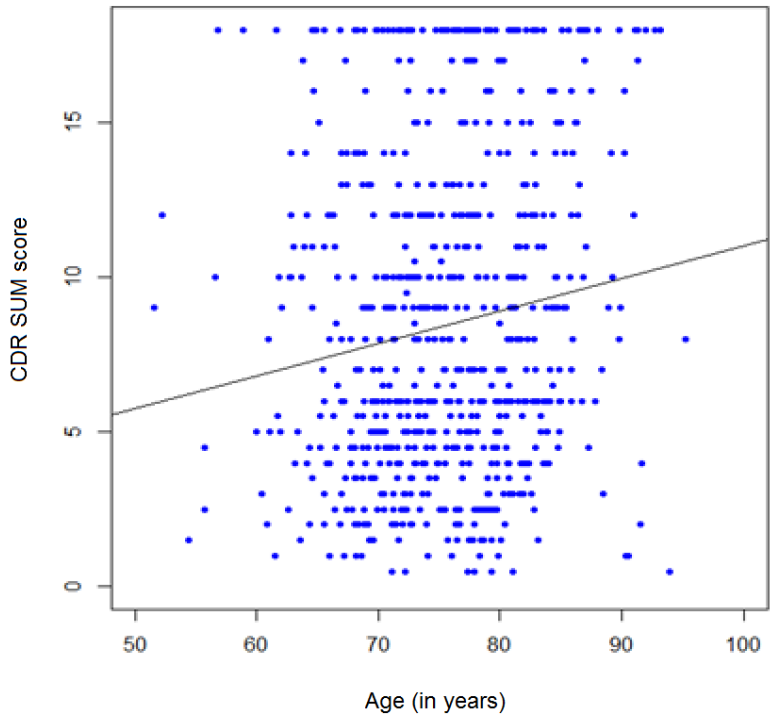

Figure 4.3. Scatter plot for CDR SUM and Age in training data

Vascular health conditions are reported as an important factor for cognitive decline. History of heart attack/cardiac arrest, transient ischemic attack, atrial fibrillation, stroke, and diabetes are selected as proxys for vascular health conditions. These four variables are in three categories: None, recent/active, or remote/inactive based on the past occurrence on the patient.

Table 4.1

Variables in the training data set (data obtained from NACC database)

Variable description	Type	Name	Codes (Values in brackets)
Time			
Duration	Derived	Duration	Derived from the birth date, visit date, and age at onset
Time-constant			
Gender	Categorical	SEX	1 (Male); 2 (Female)
Years of education	Derived	EduLevel	">=12 years" (above high school education) "< 12 years" (below high school education)
Age at onset	Derived	Ageonset	"Young" (<=66 years old) "Middle" (>66 and <=86 years old) "Old" (>86 years old)
Time-varying			
Heart attack /Cardiac arrest	Categorical	CVHATT	0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)
Transient ischemic attack	Categorical	CBTIA	0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)
Atrial fibrillation	Categorical	CVAFIB	0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)
Stroke	Categorical	CBSTROKE	0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)
Diabetes	Categorical	DIABETES	0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)
Delusion	Categorical	DEL	0 (No) 1 (Yes)
Hallucination	Categorical	HALL	0 (No) 1 (Yes)
Agitation	Categorical	AGIT	0 (No) 1 (Yes)
Depression	Categorical	DEPD	0 (No) 1 (Yes)
Anxiety	Categorical	ANX	0 (No) 1 (Yes)
Elation/euphoria	Categorical	ELAT	0 (No) 1 (Yes)
Apathy	Categorical	APA	0 (No) 1 (Yes)
Disinhibition	Categorical	DISN	0 (No) 1 (Yes)
Irritability	Categorical	IRR	0 (No) 1 (Yes)
Motor disturbance	Categorical	MOT	0 (No) 1 (Yes)
Night time behavior	Categorical	NITE	0 (No) 1 (Yes)
Appetite/eating change in type of food	Categorical	APP	0 (No) 1 (Yes)

We selected the variables based on the analysis of past studies and also the availability of measurements (Table 4.1). The objective variable is CDR SUM score. It is a comprehensive

indicator of cognition wellbeing. The six dimensions including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care are scored respectively to construct the overall CDR table. The value "0" indicates no cognitive impairment, and "3" is the most severe stage of dementia. A semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member) is set up for rating the CDR scores. It should be noted that the assessment is based on the patient's cognitive ability to function in these areas. If they are limited in performing activities at home because of physical frailty, this should not affect their scoring on the CDR that again should be rated on their cognitive ability alone.

Many studies reported that existence of neuropsychiatric symptoms is a strong indicator of fast cognitive decline. The presence of neuropsychiatric symptoms is systematically assessed by the Neuropsychiatric Inventory, which is a fully structured informant-based interview. Ten neuropsychiatric symptom domains are evaluated: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior (Appendix D).

Figure 4.4 is the panel plot for CDR SUM score and duration in different diagnosis groups. However, the diagnosis of the type of dementia is not selected as a predictor variable because the diagnosis accuracy is not good enough to group the subjects. 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 in a study and stated that 10% to 20% of patients clinically diagnosed with AD do not have AD pathology. Mixed dementia is another reason that makes diagnosis group is not favorable for patient classification. A sample study by Schneider et al. (2007) showed that

among community-dwelling older people with dementia, 54% of them have pathological evidence of one or more coexisting dementias. All of these factors make it difficult to make rigorous diagnosis classifications.

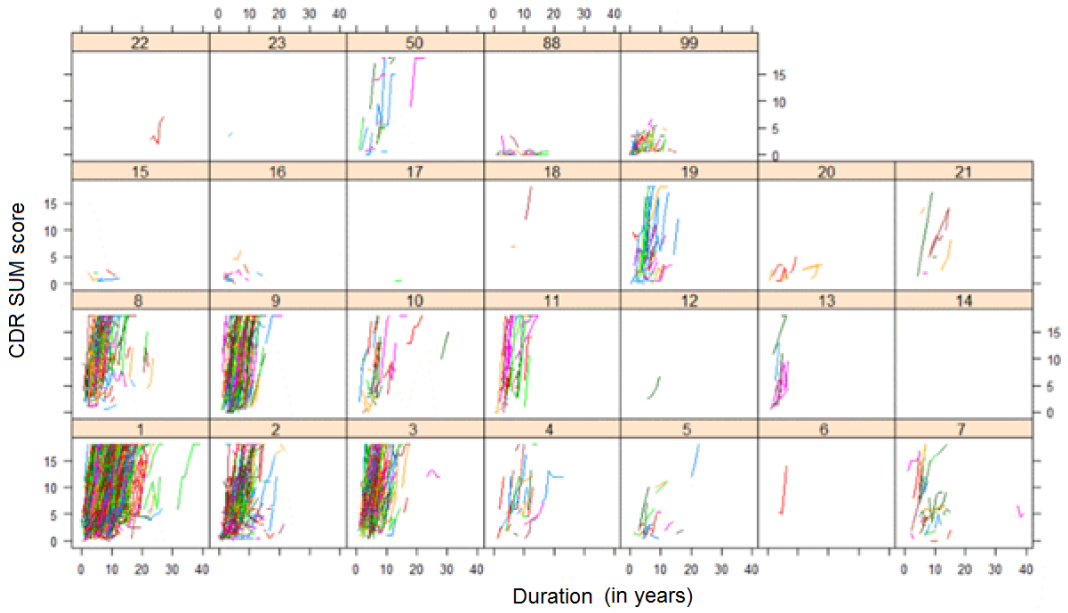

Figure 4.4. Panel plots for CDR score trajectory in different diagnosis types in training data The diagnosis codes in the plot are: 1. probable Alzheimer's disease; 2.possible Alzheimer's disease; 3. dementia with Lewy bodies; 4. probable vascular dementia; 5. Possible vascular dementia; 6. alcohol-related dementia; 7. dementia of undetermined etiology; 8. frontotemporal dementia; 9. primary progressive aphasia; 10. progressive supranuclear palsy; 11. corticobasal degeneration; 12. Huntington's disease; 13. prion disease; 14. cognitive dysfunction from medications; 15. cognitive dysfunction from medical illness; 16. Depression; 17. other major psychiatric illness; 18. Down syndrome. 19 = Parkinson's disease; 20 = Stroke; 21 = Hydrocephalus; 22 = Traumatic brain injury; 23 = CNS neoplasm; 50 = Other cognitive condition; 88 = Not applicable; 99 = Missing/unknown

4.1.2. Exploratory data analysis

The mean of duration was 8.2 years, with standard deviation of 3.9 years. The range of duration was 0.2 to 39.3 years. The mean age at onset was 70.4 years old when the first cognitive decline symptom occurred, with standard deviation of 10.8 years. The range of age at onset in this study was from 29 years to 103 years (Figure 4.5).

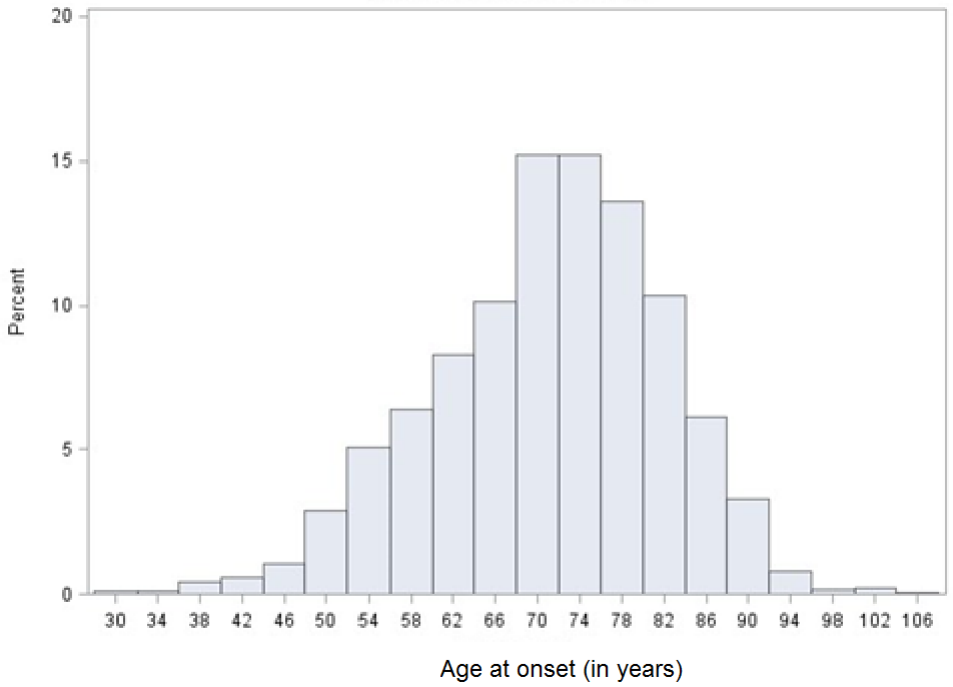

Figure 4.5. Histogram of age at onset in training data

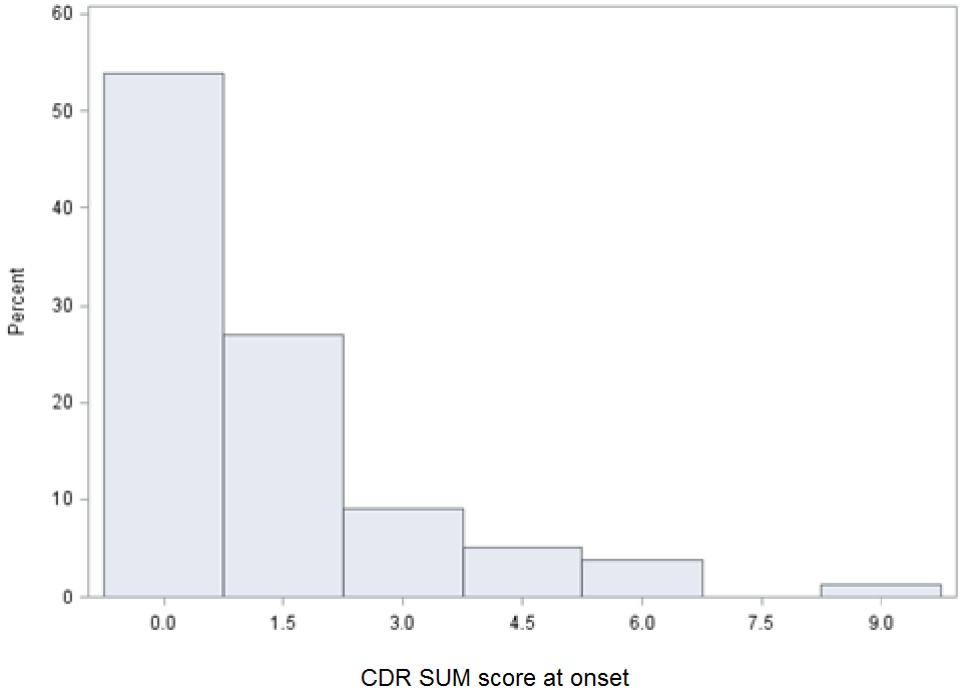

Figure 4.6. Distribution of CDR SUM score at onset in training data

Figure 4.6 shows that about 54% of the subjects who have their visit in their first year of cognitive decline are assessed as CDR SUM=0; 26% of them are assessed as 1.5; 9% of them are 3.0; the rest have 4.5 or higher CDR SUM score.

There are several ways to test if a factor is significant to a response variable. However, different tests can be used under different circumstances. CDR SUM scores from the observations are more uniformly distributed than normally distributed (Figure 4.4), we can evaluate if Least Square (LS)-means of CDR SUM score are equal. When one factor is tested, LS-means are adjusted for the other effects in the model, which means they estimate the marginal means for a balanced population. Although both z-test and t-test can test the difference in means from two groups, and both tests all assume that the observations are independently drawn from a normal distribution with unknown mean, z-test is appropriate when the variance is known, while t-test is good when variance is unknown. Chi-squared test is appropriate for testing qualitative data, in which response variable is also categorical.

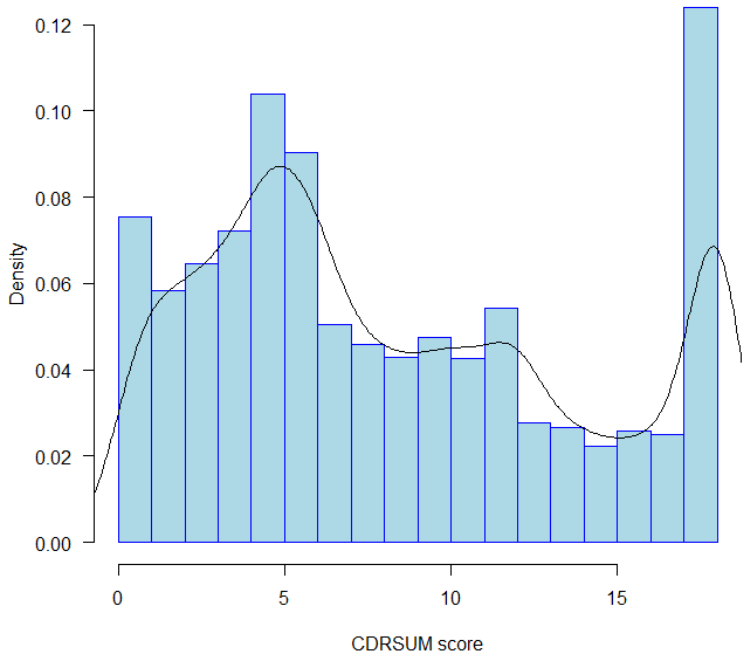

Figure 4.7. Histogram for CDR SUM scores

In the training data, there were 1,595 (59.76%) male patients. Table 4.2 shows the patient characteristics in three levels of age at onset: young, middle and old. The table summarizes the number of subjects who have vascular health problems or neuropsychiatric symptoms in their last visit to the NACC centers and the percentage of subjects in each category. The majority of the subjects in training data have their cognitive decline onset from 66 to 86 years old. However, it should be noticed that nearly one third of them have early onset (younger than 66 years old). For the factor of education level, the training data shows unbalanced design, with over 93% of the subjects having more than 12 years' education. The percentage of absence of apathy is relatively lower, only as 33.85% of the subjects having young age at onset (<=66 years old) do not have apathy. Furthermore, the prevalence of agitation is relatively high- nearly half of all the subjects have agitation (43.5%). The presence of motor disturbance is very high among subjects with young age at onset (43.6%), but low in subjects with old age at onset (8.3%). Elation is not common in the three groups of age at onset, and only about 6% of the total subjects have elation in their last visit.

Table 4.2

Characteristics of selected patients in NACC database, Sep 2005-Sep 2015

Patient Characteristics	**Ageonset**			**Total N (%)**
	Young (<=66 years old)	Middle (66,86]	Old (>86 years old)	
Male, %	559(64.25%)	978(58.67%)	58(43.94%)	1595(59.76%)
EduLevel >=12 years, %	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%)**

4. 2. Data Application

In the following sections, six strategies are applied to the training data to generate models that can be used to interpret the relationship between CDR score and the predictors.

4.2.1. Linear regression model

We start to apply strategies of model building by the simplest linear regression model. The outcome variable is the CDR SUM score, while the predictors are age at onset, education level, sex, heart attack history, transient ischemic attack, arterial fibrillation, stroke, diabetes, and neuropsychiatric symptoms.

In the previous chapter, we expressed the linear model for each individual as

$$y_{ij} = \beta_0 + \beta_{1i} t_{ij} + \sum_{q=1}^{c} \theta_k \, x_{iq} + \sum_{l=1}^{d} \mu_l \, z_{ijl} + \epsilon_{ij}$$

$$\beta_{1i} \sim N(0, \sigma_{\beta_1}^2)$$

$$\epsilon_{ij} \sim N(0, \sigma_{\varepsilon}^2) \qquad (4.\ 1)$$

where y_{ij} is the CDR SUM score for subject i at time j, β_0 is the fixed intercept and and β_{1i} are random individual slope of the *i*th subject. t_{ij} are the durations since onset of cognitive decline for subject *i* at time *j*. X_{iq} is a *c* dimension time-constant covariant matrix for subject *i* at all times. Z_{ijl} is a *d* dimension time-varying covariant matrix for subject *i* at time *j*. Z_{ijl} includes all the changing features of subject *i* at time *j*. The slope β_{1i} and error term ϵ_{ij} are assumed to follow a normal distribution, with a consistent variance of $\sigma_{\beta_1}^2$ and σ_{ε}^2 ,respectively.

The first step is to decide which variables are going to enter the model. We have to make sure all the chosen variables are significant enough to have influence on the predicted results. The model above assumes Duration (duration between time of visit and age at onset) is the most significant factor for CDR score. Figure 4.8 shows that generally CDRSUM shows an upward trend along with Duration. Obviously, several observations were scattered right below the corner of the plot. In the linear regression model, linear items of other predictors other than time and the residual part in the model would explain the variation in the plot.

Let $x_1, x_2, x_3 \ldots x_k$ be the set of *k* predictors that are related to response variable Y_{ij}, the linear regression model for subject i at a fixed time *j* has the form:

$$Y_{ij} = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k + \epsilon_{ij} \qquad (4.\ 2)$$

where ϵ_{ij} is random errors and $\beta_1, \beta_2, \beta_3 \ldots \beta_k$ are fixed regression coefficients. It is assumed that:

$$E(\epsilon_{ij}) = 0, Var(\epsilon_{ij}) = \sigma^2, Cov(\epsilon_{ij}, \epsilon_{ik}) = 0, \forall j \neq k$$

The model was fitted in R 3.25. The parameters of the full model are as in Table 4.3.

Table 4.3

Parameters of the full model

	Value	Std.Error	DF	t-value	p-value
(Intercept)	-0.63	0.57	6925.00	-1.11	0.27
DURATION	0.93	0.05	6925.00	20.01	0.00
AgeonsetOld	0.86	0.54	2664.00	1.59	0.11
AgeonsetYoung	0.18	0.30	2664.00	0.60	0.55
EduLevel>=12 years	-0.45	0.37	2664.00	-1.20	0.23
SEX	0.24	0.28	2664.00	0.87	0.39
CVHATT	-0.28	0.08	6925.00	-3.54	0.00
CVAFIB	0.06	0.06	6925.00	0.95	0.34
CBSTROKE	0.10	0.06	6925.00	1.69	0.09
CBTIA	0.05	0.04	6925.00	1.40	0.16
DIABETES	0.38	0.17	6925.00	2.17	0.03
DEL	0.53	0.10	6925.00	5.27	0.00
HALL	1.51	0.12	6925.00	12.73	0.00
AGIT	0.64	0.08	6925.00	8.11	0.00
DEPD	-0.31	0.08	6925.00	-3.94	0.00
ANX	0.08	0.08	6925.00	1.00	0.32
ELAT	-0.09	0.15	6925.00	-0.58	0.56
APA	0.60	0.07	6925.00	8.09	0.00
DISN	0.05	0.09	6925.00	0.52	0.60
IRR	-0.45	0.08	6925.00	-5.68	0.00
MOT	0.96	0.08	6925.00	11.46	0.00
NITE	0.33	0.08	6925.00	4.32	0.00
APP	0.40	0.07	6925.00	5.30	0.00
DURATION:AgeonsetOld	-0.05	0.08	6925.00	-0.61	0.54
DURATION:AgeonsetYoung	-0.03	0.03	6925.00	-0.90	0.37
DURATION:SEX	0.17	0.03	6925.00	5.72	0.00

As shown in Table 4.3, 11 variables have a high p-value (> 0.05). This indicates the variables in this linear regression model are not significant predictors. We do backward selection to eliminate the variables to fit the linear regression model. Table 4.4 is the final model that has all the predictive variables with a p-value smaller than 0.05. The predictors are duration, sex,

heart attack, stroke, diabetes, delusion, hallucination, agitation, depression, apathy, irritation, motor disturbance, night time behavior, appetite change, and the interaction term of duration and sex.

Table 4.4

Parameters of final linear regression model

	Value	Std.Error	DF	t-value	p-value
(Intercept)	-0.98	0.42	6932.00	-2.37	0.02
DURATION	0.92	0.04	6932.00	21.20	0.00
SEX	0.29	0.28	2667.00	1.05	0.30
CVHATT	-0.26	0.08	6932.00	-3.31	0.00
CBSTROKE	0.12	0.06	6932.00	2.12	0.03
DIABETES	0.38	0.17	6932.00	2.18	0.03
DEL	0.54	0.10	6932.00	5.42	0.00
HALL	1.51	0.12	6932.00	12.80	0.00
AGIT	0.65	0.08	6932.00	8.26	0.00
DEPD	-0.30	0.08	6932.00	-3.82	0.00
APA	0.61	0.07	6932.00	8.26	0.00
IRR	-0.44	0.08	6932.00	-5.61	0.00
MOT	0.96	0.08	6932.00	11.59	0.00
NITE	0.33	0.08	6932.00	4.41	0.00
APP	0.40	0.07	6932.00	5.36	0.00
DURATION:SEX	0.17	0.03	6932.00	5.77	0.00

4.2.2. Polynomial regression model

From our patients' records of CDR SUM score changes, we can see that the change of CDR SUM score along with time is not simply a linear relationship (Figure 4.6). There are fluctuations, reversion, and steadiness at some time points. A polynomial regression model is an efficient tool to present a nonlinear growth curve by modeling how variables drive responses and the direction of the responses. Quadratic or cubic relationship between CDR SUM score and time could capture the turns in the curves and further describe how much the CDR SUM score changes with respect to time.

In the polynomial regression model in Equation 3.2, P is the degree of the polynomial function. P=2 and P=3 were fitted to the model respectively.

$$y_{ij} = \beta_0 + \sum_{p=1}^{P} \beta_{pi} t_{ij}^{p} + \sum_{q=1}^{c} \theta_k \, x_{iq} + \sum_{l=1}^{d} \mu_l \, z_{ijl} + \epsilon_{ij} \qquad (3.\ 2)$$

$$\beta_{pi} \sim N(0, \sigma_{\beta_p}^2)$$

$$\epsilon_{ij} \sim N(0, \sigma_{\varepsilon}^2)$$

x_{iq} is a c dimension time-constant covariant matrix for subject *i* at all times. We choose gender, education level, and age at onset as the three time-constant covariance ($q \in [1, 3], c = 3$). Z_{ijl} is a d dimension time-varying covariant matrix for subject *i* at time *j*. Z_{ijl} includes all the changing features of subject *i* at time *j*. Vascular health conditions and the presence of neuropsychiatric symptoms are selected to enter this matrix. Again, as we discussed in the previous chapter, the slope $\beta_{\mathrm{p}i}$ and error term ϵ_{ij} are assumed to follow a normal distribution, with a consistent variance $\sigma_{\beta_{\mathrm{p}}}^2$ and σ_{ε}^2 , respectively. For notation purposes, the quadratic model would be denoted as M2, and the cubic model would be denoted as M3.

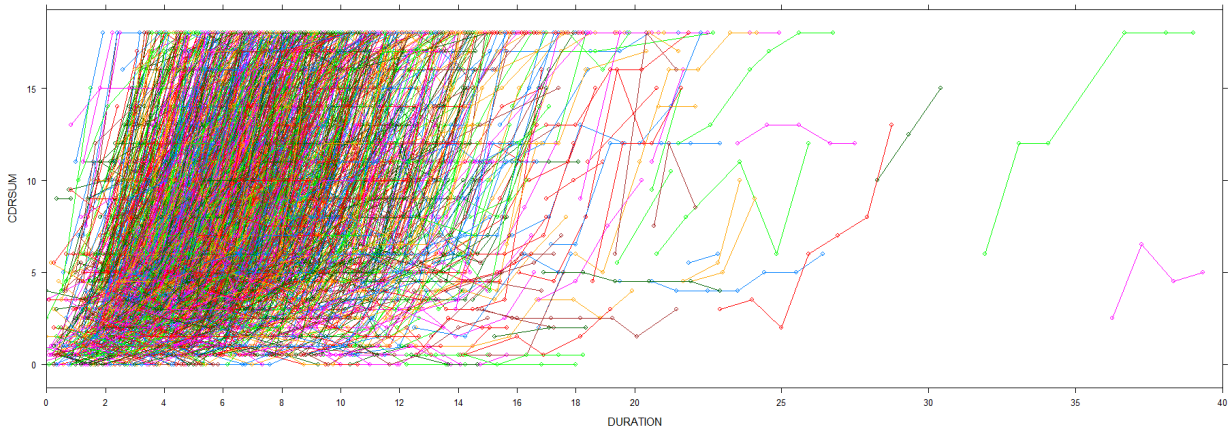

Figure 4.8. Line chart for patients with heterogeneous types of cognitive decline
X-axis is the duration from age at onset to the time of visit. Y-axis is CDR SUM score.

All of the factors including time, time constant, and time varying factors are regarded as fixed effect factors. As fixed effect factors, they are assumed to have a fixed influence on the objective function. For example, if SEX equals 2 (male is coded as 1, and female is coded as 2) in the data for subject *i* and the coefficient for SEX is 0.5, the CDR SUM score will increase by 1. Different subject ID is considered as a random effect to encounter other factors that are not included in the fixed effects. This strategy of using polynomial terms would help to capture the subtle change in the CDR SUM score along with time.

We did not take away the factors that have high p-values in the linear regression model as Table 4.4 showed. The factors Ageonset, EduLevel, CVAFIB, CBTIA, ANX, ELAT, DISN, and the interactions between duration and ageonset, which are DURATION: AgeonsetOld and DURATION: AgeonsetYoung. However, we cannot decide if the model is adequate solely based on the p-values for each factor in the model. If the full model has a better goodness of fit and better prediction results, then we should have sufficient confidence to refer to the full model as the better model. The same evaluation criteria apply to other regression models in this study.

Table 4.5

Parameters of four polynomial regression models

Parameter	M2	M3	M2cor	M3cor
Intercept	-2.89	-2.99	-2.05	2.46
DURATOIN	1.60	1.65	1.62	1.84
$DURATION^2$	-0.04	-0.04	-0.05	0.07
$DURATION^3$		0.00		0.00
Covariates				
AgeonsetOld	1.88	1.95	1.15	1.46
AgeonsetYoung	-0.88	-0.87	-0.35	0.29
EduLevel>=12 years	-0.40	-0.40	-0.47	0.49
SEX	0.53	0.51	0.61	0.54
CVHATT	-0.27	-0.27	-0.15	0.15
CVAFIB	0.05	0.05	0.01	0.01
CBSTROKE	0.12	0.12	0.14	0.14
CBTIA	0.06	0.06	0.02	0.02
DIABETES	0.37	0.37	0.41	0.42
DEL	0.51	0.51	0.47	0.47
HALL	1.42	1.41	0.98	0.97
AGIT	0.62	0.62	0.40	0.40
DEPD	-0.30	-0.30	-0.06	0.06
ANX	0.03	0.02	0.03	0.02
ELAT	-0.14	-0.14	-0.05	0.05
APA	0.59	0.59	0.48	0.48
DISN	0.00	0.00	-0.02	0.02
IRR	-0.39	-0.39	-0.27	0.27
MOT	0.90	0.90	0.55	0.55
NITE	0.34	0.34	0.22	0.22
APP	0.41	0.41	0.33	0.34
DURATION*AgeonsetOld	-0.24	-0.25	-0.16	0.22
DURATION*AgeonsetYoung	0.14	0.14	0.11	0.10
DURATION*SEX	0.12	0.12	0.09	0.10

4.2.3. Multilevel model

In this study, we assume that patients share similar cognitive decline trajectories (i.e. CDR SUM scores pattern of change) if they have the same profile in the factors that we selected for model building. It is believed that there is a law of how CDR SUM score would change based on the characteristics of a patient. This assumption is the theory foundation for the existence of a best model for CDR SUM score estimation. The multilevel model has a further assumption that

some factors are nested within a higher level of factor. We denote the multilevel model as ML model.

In the CDR SUM score modeling, we select DURATION (which is the duration from age at onset of cognitive decline to the time of visit) as the first level effect. Other factors such as time-constant covariates and time-varying covariates are nested within the same DURATION. The residual variance consists of a between-DURATION component (the variance of the DURATION-level residuals) and a within-DURATION component (the variance of the patient-level residuals). The unobserved variables in each level of the model are assumed to result in the variance between CDR SUM score outcomes for patients who have the same value in one particular factor. For example, for patients who have the same value of "1" in "DIABETES", variance may occur because of the severity of diabetes, the type of diabetes and other nuances of different cases suffering from this disease. However, even though the multi-level can compensate the unobserved factors by variance, we still expect that by selecting the most appropriate modeling technique the variance can be reduced and accuracy of prediction can be increased. In Section 4.2.2, we already examined that the quadratic model is adequate rather than the cubic model; therefore, we selected the quadratic relationship between DURATION and CDRSUM to build the level 0 model in the multi-level modeling.

Table 4.6

Parameters of multi-level model

Parameter	Value	Std.Error	p-value	95% CI
Intercept	-1.00	0.80	0.21	(-2.56,0.56)
DURATION	1.48	0.10	0.00	(1.28,1.68)
I(DURATION^2)	-0.05	0.00	0.00	(-0.05,-0.04)
AgeonsetOld	1.17	0.60	0.05	(-0.00,2.33)
AgeonsetYoung	-0.29	0.34	0.40	(-0.96,0.38)
EduLevel>=12 years	-1.64	0.62	0.01	(-2.86,-0.43)
SEX	0.61	0.31	0.05	(0.00,1.21)
CVHATT	0.09	0.16	0.58	(-0.22,0.40)
CVAFIB	-0.04	0.12	0.75	(-0.27,0.19)
CBSTROKE	0.23	0.11	0.05	(0.00,0.45)
CBTIA	0.04	0.07	0.59	(-0.10,0.18)
DIABETES	0.80	0.34	0.02	(0.12,1.48)
DEL	0.31	0.18	0.09	(-0.05,0.66)
HALL	1.51	0.22	0.00	(1.08,1.93)
AGIT	0.06	0.14	0.67	(-0.21,0.33)
DEPD	0.06	0.13	0.66	(-0.20,0.32)
ANX	-0.03	0.13	0.82	(-0.29,0.23)
ELAT	0.42	0.31	0.17	(-0.18,1.02)
APA	0.29	0.13	0.03	(0.04,0.55)
DISN	-0.11	0.16	0.49	(-0.43,0.20)
IRR	-0.11	0.14	0.42	(-0.39,0.16)
MOT	0.60	0.16	0.00	(0.29,0.91)
NITE	0.22	0.13	0.10	(-0.04,0.47)
APP	0.33	0.13	0.01	(0.07,0.59)
DURATION:AgeonsetOld	-0.16	0.11	0.14	(-0.37,0.05)
DURATION:AgeonsetYoung	0.10	0.04	0.01	(0.02,0.18)
DURATION:EduLevel>=12 years	0.16	0.07	0.02	(0.02,0.30)
DURATION:SEX	0.09	0.04	0.01	(0.02,0.17)

From the parameters in Table 4.6, we can see that DURATION has the most significant influence on cognitive decline. The coefficient of DURATION is 1.48 with 95% confidence interval of 1.28 to 1.68. At the same time, the quadratic term I (DURATION^2) has negative effect of -0.05 on CDR SUM. Considering the rate of cognitive decline by time, we can observe the first derivative of DURATION is -0.05. This indicates that as time goes by, the deterioration rate with regard to CDR SUM score is declining. Therefore, the model shows that the typical trend of CDR SUM score is a gradually increasing curve rather than a linearly increasing one.

Among the time-constant factors, older age at onset (>86 years old) indicates faster cognitive decline with coefficient of 1.17 for variable “AgeonsetOld”, with a 95% confidence interval of 0 to 2.33. The model assumes that once cognitive decline starts in an older age (after 86 years old), probability is high that a patient suffers a faster decline. However, the decline rate, represented by CDR SUM score increment per year, varies with standard error of 0.6.

On the other hand, we also can conclude that the effect of education is significant with little exemption. The coefficient of EduLevel>=12 years is -1.64 with 95% confidence interval of -2.86 to -0.43. This finding confirms that education attainment deters the progress of cognitive decline.

Among the time-varying factors in level 2, Hallucination has the most significant indication of fast decline with coefficient of 1.51. This implies that with the presence of hallucination, Clinical Dementia Rating score will dramatically increase. Although it is not clear that which dimension of the six domains including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care would be most affected, we can still conclude that the presence of hallucination points to a fast time frame for progression to later stage of dementia.

4.2.4. Semiparametric model with time series correlation

Semiprarametric model is to some extent an extension of the multi-level model. In multi-level model, it is assumed that the variable “DURATION” plays a direct role in affecting the CDR SUM score change. Similarly, semiparametric model will adopt this assumption but consider the relationship between time and outcome to be following a curve instead of simply a quadratic relationship. The curve is a typical trajectory that the factor “DURATION” does to “CDRSUM”, and other individual characteristics would add more additional influence on

"CDRSUM". The model is featured as "semiparametric" because the curve is smoothed to be proxy for the mean population curve, and other effects are modeled by parametric function. We denote the semiparametric model with correlation as SME (w-cor) model.

There is an assumption of serial correlation between the CDR SUM score recorded of the same patient in disparate time points. We assume patients with higher CDR SUM scores are more affected by time "DURATION". The simplest and most commonly observed correlation is the first-order autocorrelation. A current observation of the error term u_t is a linear function of the previous (lagged) observation of the error term u_{t-1}. In this study, we assume the serial correlation relationship decays as time increases. The longer time intervals are, the weaker the correlation between two observed CDR SUM scores will be.

Table 4.7

Parameters of semiparametric model with correlation

Parameter	Value	Std.Error	p-value	95% CI
(Intercept)	-0.90	0.58	0.12	(-2.04,0.23)
DURATION	1.27	0.09	0.00	(1.10,1.44)
I(DURATION^2)	-0.02	0.00	0.00	(-0.03,-0.01)
AgeonsetOld	0.68	0.54	0.21	(-0.38,1.75)
AgeonsetYoung	-0.27	0.33	0.41	(-0.93,0.38)
EduLevel>=12 years	-0.67	0.32	0.04	(-1.30,-0.03)
SEX	0.53	0.30	0.08	(-0.06,1.11)
CVHATT	-0.11	0.08	0.13	(-0.26,0.03)
CVAFIB	0.01	0.06	0.80	(-0.09,0.12)
CBSTROKE	0.14	0.05	0.01	(0.04,0.25)
CBTIA	0.00	0.03	0.96	(-0.07,0.07)
DIABETES	0.44	0.17	0.01	(0.11,0.76)
DEL	0.50	0.08	0.00	(0.33,0.66)
HALL	0.98	0.10	0.00	(0.79,1.17)
AGIT	0.39	0.06	0.00	(0.27,0.52)
DEPD	-0.05	0.06	0.41	(-0.18,0.07)
ANX	0.06	0.06	0.37	(-0.06,0.18)
ELAT	-0.04	0.13	0.76	(-0.28,0.21)
APA	0.49	0.06	0.00	(0.37,0.61)
DISN	0.01	0.07	0.93	(-0.14,0.15)
IRR	-0.26	0.06	0.00	(-0.38,-0.13)
MOT	0.57	0.07	0.00	(0.43,0.70)
NITE	0.23	0.06	0.00	(0.11,0.35)
APP	0.35	0.06	0.00	(0.23,0.47)
DURATION:AgeonsetOld	-0.07	0.11	0.51	(-0.29,0.14)
DURATION:AgeonsetYoung	0.12	0.05	0.01	(0.02,0.21)
DURATION:SEX	0.11	0.04	0.01	(0.02,0.20)

We can see from Table 4.7 the parameters that “DURATION” has the most significant effects on “CDRSUM” with coefficient of 1.27. Age at onset is not a significant factor in this model. The 95% confidence intervals of both “AgeonsetOld” and “AgeonsetYoung” includes zero, therefore in this model, we cannot conclude that age at onset has positive or negative influence on CDR SUM scores. However, “HALL” and “MOT” still have significance in CDR SUM estimation. The factors having limited effects on CDR SUM scores are “CBSTROKE” and

“DIABETES”. Some factors that are significant in multi-level model are no longer significant in semiparametric model, such as “DIABETES” and “DURATION:AgeonsetYoung”.

How to interpret the significance of the factors affect “CDRSUM” depends on which model we are using. Most importantly, the coefficient for the quadratic term I (DURATION^2) is 0.07, which is positive. Therefore, the semiparametric model with correlation supports that the deterioration rate with regard to CDR SUM score is declining as time goes by.

4.2.5. Semiparametric model without time series correlation

It is not always true that there is a correlation between the observations within the same subject. In many cases, a serial correlation may not be accurate. Therefore, we also fit the semiparametric model that does not include time series correlation. We denote the semiparametric model without correlation as SME (N-cor) model.

Table 4.8

Parameters of semiparametric model without correlation

Parameter	Value	Std.Error	p-value	95% CI
(Intercept)	2.01	0.39	0.00	(1.24,2.78)
DURATION	0.20	0.09	0.03	(0.02,0.38)
I(DURATION^2)	0.07	0.00	0.00	(0.06,0.08)
AgeonsetOld	-0.72	0.34	0.03	(-1.38,-0.06)
AgeonsetYoung	0.43	0.25	0.08	(-0.06,0.91)
EduLevel>=12 years	-0.83	0.20	0.00	(-1.23,-0.44)
SEX	0.24	0.21	0.24	(-0.16,0.65)
CVHATT	-0.12	0.06	0.06	(-0.25,0.00)
CVAFIB	-0.05	0.05	0.40	(-0.15,0.06)
CBSTROKE	0.15	0.05	0.00	(0.05,0.25)
CBTIA	-0.07	0.04	0.06	(-0.14,0.00)
DIABETES	0.01	0.13	0.96	(-0.24,0.25)
DEL	0.90	0.10	0.00	(0.71,1.10)
HALL	1.36	0.12	0.00	(1.13,1.59)
AGIT	0.54	0.08	0.00	(0.39,0.69)
DEPD	-0.25	0.07	0.00	(-0.39,-0.10)
ANX	0.29	0.07	0.00	(0.14,0.43)
ELAT	0.11	0.15	0.44	(-0.18,0.41)
APA	0.80	0.07	0.00	(0.66,0.94)
DISN	0.21	0.08	0.01	(0.05,0.38)
IRR	-0.44	0.08	0.00	(-0.59,-0.30)
MOT	1.08	0.08	0.00	(0.92,1.24)
NITE	0.23	0.07	0.00	(0.09,0.37)
APP	0.62	0.07	0.00	(0.47,0.76)
DURATION:AgeonsetOld	0.20	0.11	0.06	(-0.01,0.41)
DURATION:AgeonsetYoung	-0.02	0.06	0.76	(-0.14,0.10)
DURATION:SEX	0.17	0.05	0.00	(0.06,0.27)

Table 4.8 is the list of parameters of SME(N-cor) model. We can see from the parameters that the factors are having limited effect on CDR SUM score. Some factors that are significant in multi-level model are no longer significant in semiparametric model, for example, “DIABETES” and “DURATION:AgeonsetYoung”. However, some do still have significance in CDRSUM estimation, such as “HALL” and “MOT”.

It depends on which model we are using that we can interpret the significance of the factors affect “CDRSUM”. Most importantly, the coefficient for the quadratic term I

(DURATION^2) is 0.07, which is positive. Therefore, the semiparametric model with correlation supports that the deterioration rate with regard to CDR SUM score is declining as time goes by. This conclusion contradicts the conclusion from multi-level model that the decline rate of CDR SUM score is slowing down with time. Therefore, how to interpret the significance of the factors depends on the model we are using.

4. 3. Model Selection

As discussed previously, six models were proposed to explain the relationship between CDR SUM score and other attributes of a patient with cognitive decline. Based on the assumption that there is a model describing the true relationship between the objective variable CDR SUM score and other predictive variables, we compare the models to find the best model that expresses that relationship. Model selection is about choosing a proposed model from a set of potential models with the best inductive bias. The inductive bias, also known as learning bias, is the set of assumptions that the learner uses to predict outputs, after being given inputs that the model has not encountered. These assumptions are the fundamentals for generalizing the rules observed to a larger population beyond the training data.

In practice, model selection is selecting parameters in order to create a model of optimal complexity based on given training data. This process can be completed using different criteria according to the model building techniques and assumptions of the models. Several model building techniques in model selection include defining the number of knots in regression spline, the number of neurons in a neural network chosen for optimization of model, etc. (Burnham & Anderson, 2002). The goal is to choose the optimal model that most approximates the true relationship that is hidden in the training data. However, the meaning of “optimal” or the way of approximation has to be defined first. Of course, there are many criteria to define “optimal”. An

optimal model should describe a problem in a simplified way and abstract the most eminent characteristics. Model selection strategies are of two categories: data driven (Empirical) and theory driven (Theoretical).

4.3.1. Empirical methods

One of the most widely used empirical methods for model selection is adjusted R-squared (Wherry,1931). R-squared statistic can be used to compare regression models. A model with a larger R-squared value indicates the independent variables explain a larger percentage of the variation in the independent variable. Suppose variable *y* has a set of observed values marked as y_i. The predicted value by a model for y_i is noted as $\hat{y}_i$. The residual values are $y_i - \hat{y}_i$:

$$\bar{y} = \frac{1}{n}\sum_{i=1}^{n} y_i \tag{4. 3}$$

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2} \tag{4. 4}$$

An R-squared value of 1 indicates that the regression line perfectly fits the data. R-squared gives some information about how well a model fits the data points. However, R-squared decreases if there are too many predictor variables in the model. The adjusted R-squared value takes this into account:

$$R^2_{adj} = 1 - (\frac{n-1}{n-p-1})(1 - R^2) \tag{4. 5}$$

Statistical sampling is an essential way to reduce time and cost to measure the parameters of the whole population. Random sampling with replacement is known as bootstrap. Bootstrap provides a method other than confidence intervals to estimate a population parameter (Efron, 1979). This technique can be conducted with the help of development of efficient algorithms and

computation capacity. It is heavily dependent upon computer calculations. As computing power has increased and become less expensive, bootstrap techniques have become more widespread.

Jackknife is a resampling technique especially useful for variance and bias estimation. Jackknife method systematically leaves out each observation from a dataset and calculates the estimate and then finding the average of these calculations. The jackknife estimate of a parameter can be found by estimating the parameter for each subsample omitting the ith observation y_j to estimate the previously unknown value of a parameter $y_{(\cdot)}$:

$$\widehat{y_{(\cdot)}} = (\frac{1}{n-1})^2 \sum_{i}^{n} \sum_{j \neq i}^{n} y_i \qquad (4.\ 6)$$

The jackknife technique can be used to estimate the bias of an estimator calculated over the entire sample. This provides an estimated correction of bias due to the estimation method. The jackknife does not correct for a biased sample. Instead, it is a linear approximation of the bootstrap.

Cross validation is a model evaluation method that does not use the entire data set to build the model. In cross validation, not all the available data are used to build the model, and some of the data are removed to test the performance of the learned model on these unseen data. The basic kind of cross validation is holdout method, where the data set is separated into two sets, training set and testing set. The training data only is used to fit the model. Then the model can be used to predict the output for the data in the testing set. The model depends heavily on the data points in the training set, and thus the result of model and prediction are significantly different depending on which data are included in training set and testing set. Similar methods applied in K-fold cross validation is one way to improve over the holdout method. The data set is divided into *k* subsets, and the holdout method is repeated *k* times. Each time, one of

the *k* subsets is used as the test set and the other *k-1* subsets are put together to form a training set.

4.3.2. Theoretical methods

The Akaike information criterion (AIC) is a measure of the relative quality of statistical models for a given set of data. There will always be information lost due to using a candidate model to represent the "true" model (i.e. the process that generates the data). The goal of model selection is to select the model that minimizes the information loss from among the candidate models. AIC is founded on information theory: it offers a relative estimate of the information lost when a given model is used to represent the process that generates the data.

We denote *y* as the observed data. Assume that y is to be described using a model $\boldsymbol{M_k}$ selected from a set of candidate models $\boldsymbol{M_{k1}}$, $\boldsymbol{M_{k2}}$, …, $\boldsymbol{M_{kL}}$. We also assume that each $\boldsymbol{M_k}$ is uniquely parameterized by a vector θ_k, where θ_k is an element of the parameter space Θ (k) (k∈ $\{k_1, k_2, \dots, k_L\}$).

We denote $L(\theta_k|y)$ as the likelihood for *y* based on $\boldsymbol{M_k}$, represented as

$$L(\theta_k|y) = f\ (y|\theta_k) \tag{4. 7}$$

Assuming that there exists a true parameter vector θ_k^* that defines the true model $\boldsymbol{M}_k^*$. We wish to select θ_k, which is the closest to the true parameter θ_k^* based on the observed data.

Kullback–Leibler divergence from $\boldsymbol{M}_k^*$ to $\boldsymbol{M_k}$, denoted as $D_{KL}(\boldsymbol{M}_k^* \| \boldsymbol{M_k})$, is the amount of information lost when $\boldsymbol{M_k}$ is used to approximate $\boldsymbol{M}_k^*$(Burnham and Anderson, 2002):

$$D_{KL}\ (\ \boldsymbol{M}_k^*\ \|\boldsymbol{M_k}\ ) = \int \{\log f(y|\theta_k^*) - \log f(y|\theta_k)\} \log f(y|\theta_k^*)\, dy \tag{4. 8}$$

By minimizing $D_{KL}(\boldsymbol{M}_k^* \| \boldsymbol{M_k})$, we can find the best model that is closest to the true model $\boldsymbol{M}_k^*$.

Since the first term $\int\{\log f(y|\theta_k^*)\}\log f(y|\theta_k^*)\,dy$ is constant over all models, we instead maximize:

$$H(\theta_k) = \int\{\log f(y|\theta_k)\}\log f(y|\theta_k^*)\,dy \tag{4. 9}$$

$f(y|\hat{\theta}_k)$ is the maximum likelihood estimate for Model $\boldsymbol{M_k}$.

Model selection is based on Akaike's selecting the model that produces largest $E_{\theta_k^*}H(\hat{\theta}_k)$ among the competing models. The log likelihood equation evaluated at the maximum likelihood estimate under model $\boldsymbol{M_k}$:

$$\log f(y|\hat{\theta}_k) = \sum_{i=1}^{n} f(y_i|\hat{\theta}_k) \tag{4. 10}$$

Akaike found that $E_{\theta_k^*}\ \log f(y|\hat{\theta}_k) - E_{\theta_k^*}H(\hat{\theta}_k) \approx k$, where k is the number of free parameters to be estimated. After penalizing for larger values of k, Akaike Information Criteria:

$$\text{AIC} = -2lnf(y|\hat{\theta}_k) + 2k \tag{4. 11}$$

Applying AIC in practice is to find the models' corresponding AIC values for a set of candidate models. Given a set of candidate models for the data, the preferred model is the one with the minimum AIC value. AIC rewards goodness of fit (as assessed by the likelihood function), but it also includes a penalty that is an increasing function of the number of estimated parameters. The penalty discourages overfitting, because increasing the number of parameters in the model almost always improves the goodness of the fit.

The motivation behind BIC can be seen through a Bayesian development of the model selection problem. The detailed derivation process is included in Appendix C. $\pi(k)$ (k $\in$ $\{k_1, k_2, \ldots, k_L\}$)denote a discrete prior over the models $\boldsymbol{M_{k1}}$, $\boldsymbol{M_{k2}}$, …, $\boldsymbol{M_{kL}}$, and $f(\theta_k|k)$ denote a prior on θ_k given the model $\boldsymbol{M_k}$ (k $\in \{k_1, k_2, \ldots, k_L\}$). The candidate or approximating model is $f(y|\theta_k)$, and the candidate class are :

$$\mathbb{F}(k) = \{f(y|\theta_k)|\theta_k \in \Theta\ (k)\} \quad (4.\ 12)$$

$f(y|\hat{\theta}_k)$ is the fitted model, *y* is denoted the observed data, and n is the sample size.

Bayesian (Schwarz) information criterion (BIC) is expressed as:

$$\text{BIC} = -2lnL\left(\hat{\theta}_k\middle|y\right) + kln(n) \quad (4.\ 13)$$

4.3.3. Compromised evaluation criteria for model selection

In this study, empirical and theoretical methods are both used as compromised methods in model selection.

The AIC and BIC criteria are used for comparing models that have the same number of parameters. In general, models chosen by BIC will be more parsimonious than those chosen by AIC. Among the six strategies we examined in this chapter, only the nonlinear growth of quadratic model and its counterpart with correlation have the same number of parameters. The same with the nonlinear growth of cubic models. Therefore, it is meaningful to compare those who share the same number of parameters. Table 4.9 lists the AIC and BIC for the models except semiparametric ones. Analysis was implemented in R 3.2.5.

Table 4.9

The AIC and BIC for five models

Description	Model	AIC	BIC
Linear model	M1	51978.33	52179.05
Nonlinear growth: quadratic model	M2	51556.65	51764.53
Nonlinear growth: cubic model	M3	51573.49	51788.53
Nonlinear model with correlation: quadratic	M2cor	49715.1	49930.15
Nonlinear model with correlation: cubic	M3cor	49718.81	49941.02
Multilevel model	M4	49826.27	50170.25

In order to examine the goodness-of-fit for the mixed models, R-squared (R^2, also known as coefficient of determination) was used as the first measurement of model goodness-of-fit statistics. R-squared is widely used for linear regression model for examining how well the

model fits the data. However, R-squared is only appropriate in a linear regression model. Therefore, the linear model of fitted and observed values as shown in Equation 3.22 was made and then the R-squared in Equation 3.23 was evaluated for this linear model. R-squared measures the proportion of the observed value variation that can be explained by the linear model. The second measurement is the correlation coefficient between the fitted and the observed values, as shown in Equation 3.24. The higher the correlation, the better the fitted values from a certain model simulate the observed value.

MSE(N-cor) model had correlation coefficient of 0.93 and R-squared of 0.86. SME(w-cor) had correlation coefficient of 0.73 and R-squared 0.53, while multilevel (ML) model had correlation coefficient of 0.52 and R-squared 0.27. The SME model without random effect correlation fits remarkably well to the training data, with correlation of 0.93 between fitted value and observed value. Hypothesis that CDR SUM within the same subject would have exponential correlation was not supported. The residual plot for MSE(N-cor) model is approximately normally distributed, indicating the model is adequate. MSE(N-cor) model is preferred over MSE(w-cor) model or multilevel model. Therefore, SME(N-cor) model was selected for prediction.

To show the predictions from each model, we randomly selected four patients to make predictions. Figure 4.8 and Figure 4.9 are the prediction results from ML model and SME(N-cor) model, respectively. The records for the four patients are as attached excel files.

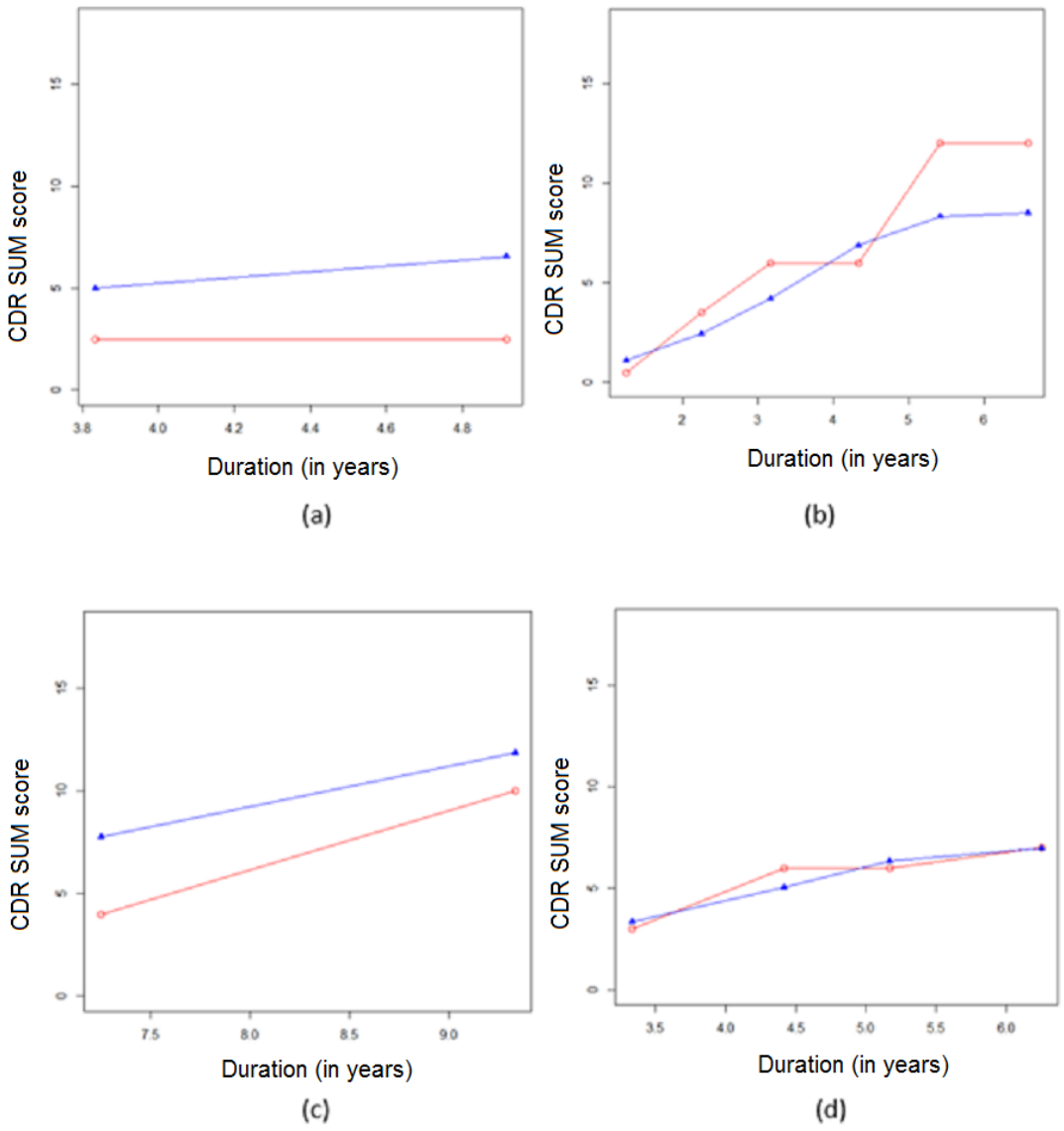

Figure 4.9. The prediction results for Strategy 4 (Multilevel model)
Red circles are the actual observed CDR SUM score, and blue triangles are the predicted values by multilevel model. (a) (b) (c) (d) are the results for the 4 patients respectively.

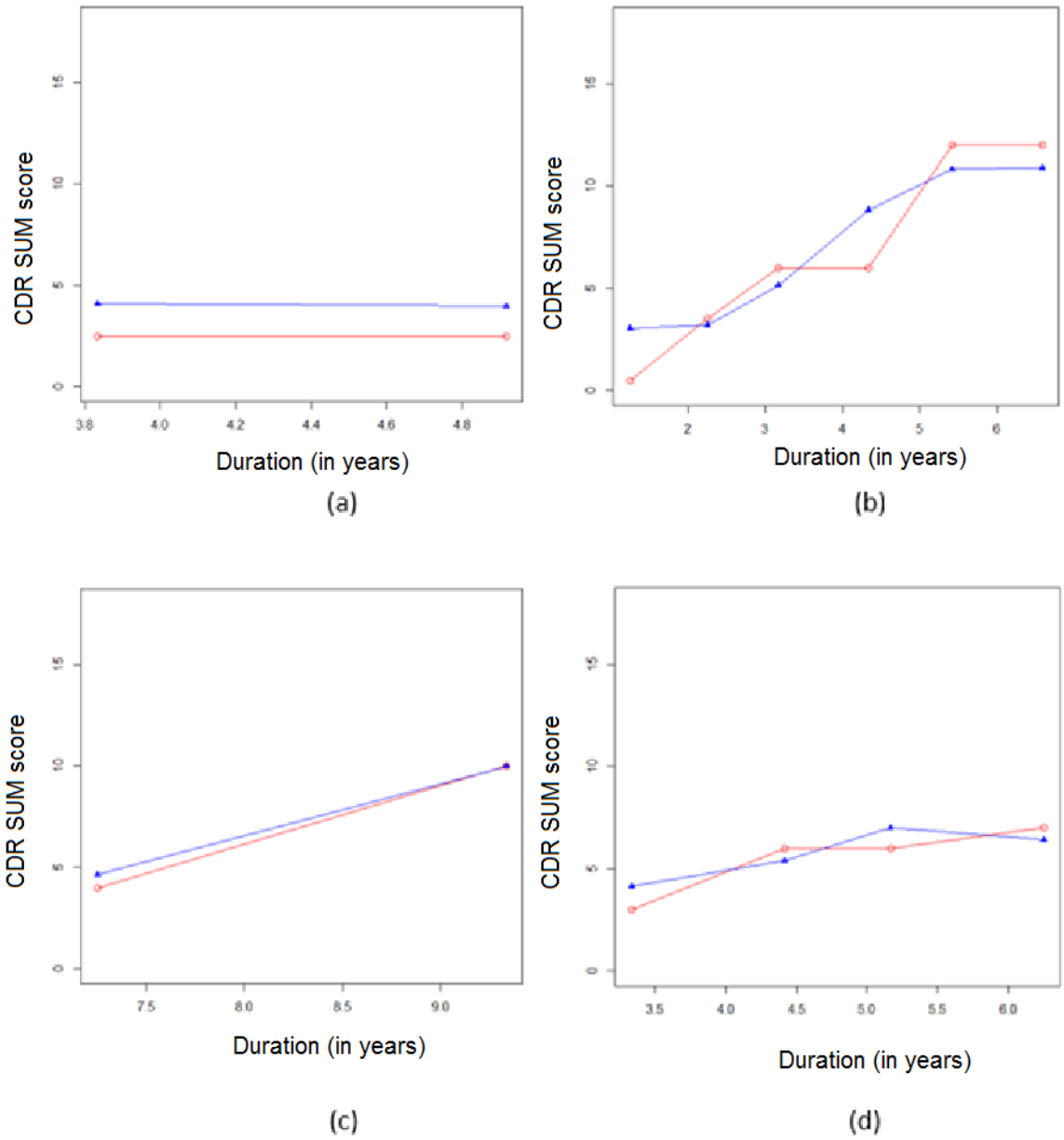

Figure 4.10. The prediction results for Strategy 6 (Semiparametric model without correlation) Red circles are the actual observed CDR SUM score, and blue triangles are the predicted values by SME-Ncor model. (a) (b) (c) (d) are the results for the 4 patients respectively.

4. 4. Test Data

Test Data is a separate dataset from training data that would fit into the proposed model and test if the model makes robust predictions. The testing data are extracted from the NACC UDS dataset from Sep 2005 to Dec 2015. The subjects are all Caucasians who are alive until the

time of data acquisition in Dec 2015. Those who have at least four visits to the NACC centers are included, and those who have missing values in any variables in age at onset, education level, sex, heart attack history, transient ischemic attack, arterial fibrillation, stroke, diabetes, and neuropsychiatric symptoms are excluded from the test data. The test data after cleaning consists of 2,996 subjects and 16,783 observations.

4. 5. Test Model Robustness

To test if the model is robust, we use bootstrap to select testing samples from the testing data. 5000 observations were randomly drawn 10 times from the testing data pool and were entered in both SME models. Linear regression model for predicted CDR SUM by SME(N-cor) model and observed CDR SUM was fitted. Then R-squared of the linear model and correlation between predicted CDRSUM by SME(N-cor) model and observed CDR SUM were assessed. Table 4.10 shows the ten testing results. Figure 4.10 shows the box plots for the R-squared and correlation coefficient results by both models. The results were stable, and again, prediction from SME(N-cor) model had significantly better performance than SME(w-cor). For SME(N-cor) model, the mean of R-squared was 17% (variance of 6.67E-05), indicating about 17% of the variance of observed CDR SUM score can be explained by predicted scores of the model (or vice-versa). The mean of correlation between predicted CDR SUM and observed CDR SUM was 0.41 (variance of 9.50E-05). Although the positive correlation is moderate, it is a high correlation in a human related study. It should be kept in mind that correlation coefficient is very sensitive to outliers. Therefore, the SME(N-cor) model is considered to be representative of typical dementia progression processes, and it is selected for further analysis.

Table 4.10

Ten testing results

	R-squared		Correlation	
Random trials	SME(N-cor)	SME(w-cor)	SME(N-cor)	SME(w-cor)
1	0.17	0.16	0.42	0.40
2	0.16	0.16	0.41	0.39
3	0.16	0.15	0.40	0.39
4	0.16	0.16	0.41	0.39
5	0.18	0.17	0.42	0.41
6	0.17	0.16	0.41	0.40
7	0.17	0.16	0.41	0.40
8	0.17	0.16	0.41	0.40
9	0.19	0.18	0.44	0.42
10	0.16	0.15	0.40	0.39
Average	0.17	0.16	0.41	0.40

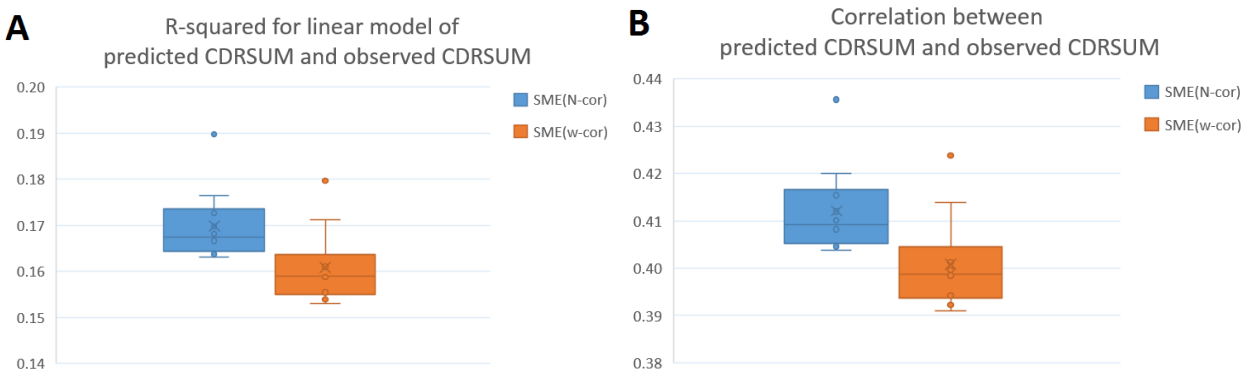

Figure 4.11. (A and B) Testing results by SME models
Blue box represents the testing results of semiparametric model without correlation. Orange box shows the results of semiparametric model with correlation. The bars represent the estimated value, and the blue and gray area are the lower and upper range of estimation with 95% confidence interval.

Figure 4.11 shows the estimated coefficients for SME(N-cor) model. Neuropsychiatric symptoms including delusion, hallucination, agitation, anxiety, apathy, disinhibition, motor disturbance, and appetite change (eating change in type of food) were all indicators of higher CDRSUM score. History of stroke presence and night time behavior (awakening during the

night, rising too early or taking excessive naps during daytime) had smaller impacts on increasing CDR SUM score. Furthermore, along with time, female gender (codes=2) showed higher CDR SUM score than male counterpart. This could be the result of longer survival time for females.

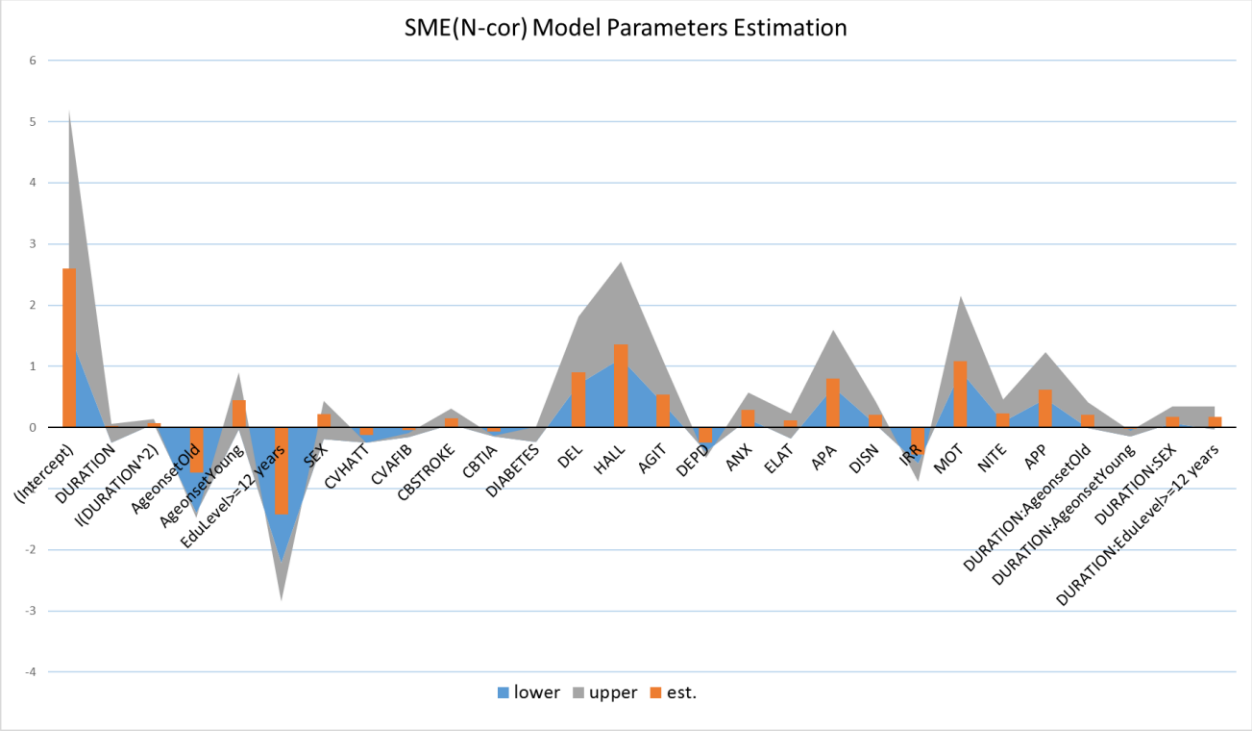

Figure 4.12. Estimated coefficients for SME(N-cor) model

It can be identified that older age at onset (>86 years old), education beyond high school education (>=12 education years), and presence of irritation were indicators that bring down the CDR SUM score. Education level was the most influential factor among these three indicators with a peak of -2.8. Depression had minimal negative effect on CDR SUM score, which could be due to shorter survival time for patients with depression.

Among the factors we tested in SME(N-cor) model, there is little evidence that young age at onset (≤66 years old), sex, heart attach/cardiac arrest, atrial fibrillation, transient ischemic

attack, diabetes, presence of elation, the interaction between duration and age at onset, and the interaction between duration and education level are significant ($p>0.05$).

According to NIH Office of Science Education (2009), the gene for apolipoprotein E (APOE) comes in three varieties (alleles): E2, E3, and E4. While E2 protects a person from developing Alzheimer's disease, E4 increases the chances of developing it. Humans inherit one copy of the APOE gene from each of their biological parents. The APOE genotype alone does not determine whether a person will develop Alzheimer's disease, though. About 30 percent of Alzheimer's disease patients have at least one copy of E4, but about 30 percent of people with the disease do not have a copy of E4. Therefore, people without E4 may still get Alzheimer's disease, and people with E4 may never get it. The performance of the model would decrease 50% if categorical factor of APOE ε4 is added into the model while the goodness of fit still maintains as good not including it. This could be because the distribution of APOE ε4 alleles in the training data are not consistent within the population and caused overfitting of the model. Figure 4.12 shows the histogram of the APOE genotype recorded in training data, from NACC database. Table 4.11 is the approximate distribution of APOE genotype in human population. However, there was a certain pattern of CDR SUM score associated with APOE genotype in the training data.

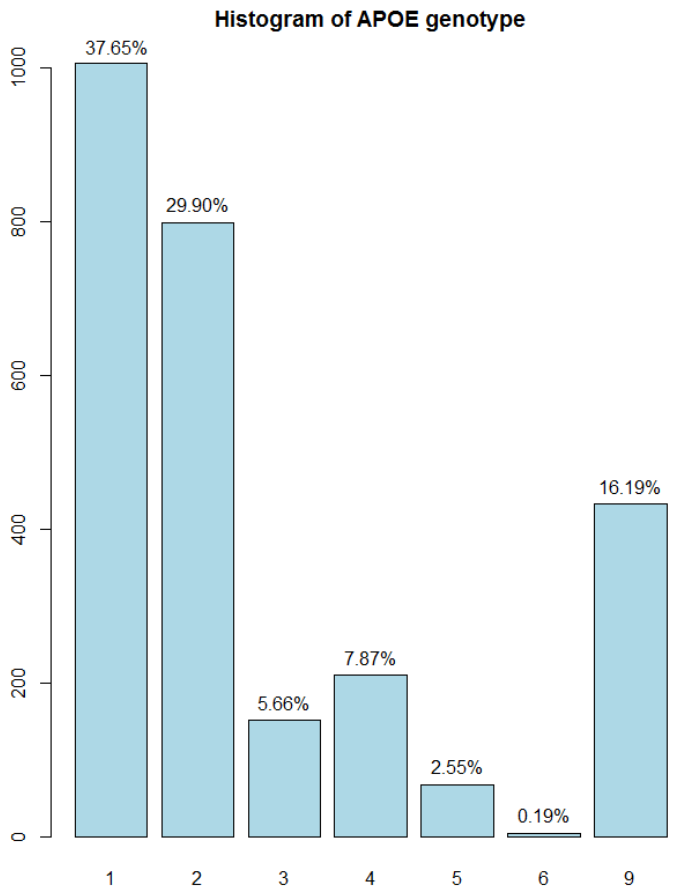

Figure 4.13. The histogram of the APOE genotype recorded in training data (from NACC database). Codes are as following: 1= e3, e3; 2 = e3, e4; 3 = e3, e2; 4 = e4, e4; 5 = e4, e2; 6 = e2, e2; 9 = missing/unknown/not assessed

Table 4.11

Approximate distribution of APOE genotype in human population

APOE genotype	Percent in Population	Effect on Person
1= e3,e3	55%	Normal(baseline) chance of developing AD
2 = e3,e4	25%	3 to 5 times greater chance of developing AD
3 = e3,e2	15%	Decreased chance of developing AD
4 = e4,e4	1-2%	15 times greater chance of developing AD
5 = e4,e2	1-2%	Normal(baseline) chance of developing AD
6 = e2,e2	1-2%	Decreased chance of developing AD

Source: NIH Office of Science Education,
Link: https://science.education.nih.gov/supplements/nih9/bioethics/guide/pdf/Master_4-2.pdf

The findings from Semiparametric mixed effect model provide more accurate information about the course of cognitive decline. Moreover, SME(N-cor) model provides a solid tool for CDR SUM score estimation for patients with cognitive decline. The prediction results by two SME models indicate that not incorporating longitudinal correlation would improve prediction accuracy. Both SME models with and without correlation had better fit and better prediction results than ML model. Our study reveals that dementia severity along with time can be predicted using demographic and clinical characteristics of patients. The model developed in this study may apply for clinical monitoring, dementia prognosis and reference for medical trials, as patient-specific trends can be obtained.

4. 6. Apply Semiparametric Method to Lewy bodies Dementia Group

The previous analysis was performed based on the assumption that there is little difference in CDR SUM score trajectory among various diagnosis groups. However, it is not quite realistic that all dementia types share the same progression course in the terms of CDR SUM score, even though it is commonly agreed that high accuracy diagnosis is hard to make until post mortems autopsy. In NACC data, four sections are evaluated for reach diagnosis conclusion: cognitive and behavioral status, cerebrospinal fluid (CSF) Biomarkers, imaging evidence and genetic mutations, and etiological diagnoses. Of 2,669 patients, 825 (31%) had at least one diagnosis result changed from the previous visit. In the following section, we further assume that the last diagnosis is the closest to the true diagnosis that can be found in autopsy.

This assumption allows us to classify the patients into different dementia types instead of analyzing cognitive decline trajectory as a whole. From the previous section, we already know that the simulation results and prediction results are better for semiparametric model without

correlation. Therefore, we will apply the semiparametric model to a specific type of dementia that is sorted in the NACC data.

The training data was requested in October 2015, and the testing data was requested in June 2016. Due to the time difference of acquiring the data, we have different diagnosis codes in training data and testing data because of version updates from V2 to V3. The version changes of NACC data include the change of diagnosis codes as well. The previously named "NACCPRET" which is a derived variable for primary etiological diagnosis was recoded as "NACCETPR". The allowable codes were changed accordingly. For example, in NACC UDS V2, the diagnosis codes included "1 = Probable Alzheimer's disease", "2 = Possible Alzheimer's disease", and "3 = Dementia with Lewy bodies". In latest version V3, there is no more "Probable" or "Possible" description. The latest diagnosis codes are "1 = Alzheimer's disease (AD) 2 = Lewy body disease (LBD) 3 = Multiple system atrophy (MSA)". The four most common types of dementia are AD, Lewy bodies, Frontomental dementia and vascular dementia. However, in V2 there are separate categories for "Probable" and "Possible" Alzheimer's disease, and in V3 there was only one code for Alzheimer's disease. The same applies to is the case with vascular dementia. In V3, frontomental dementia is divided into "FTLD with motor neuron disease (e.g., Amyotrophic lateral sclerosis (ALS))" and "FTLD, other".

Based on the diagnosis record of the very last visit, we classify the patients as different diagnosis groups. Those who had Lewy bodies were screened from all the subjects to be a best group to test the model for a specific type.

There were 730 patients who had the last diagnosis as "Lewy bodies" in our requested data. Of them, 311 were deceased that can be used as training data in model building, 419 were alive, with 1559 observations, that are separated as testing data to verify the model

robustness.Figure 4.13 represents the histogram for oserved CDR SUM scores in Lewy bodies dementia group. Table 4.12 shows the parameters of the semiparametric model for Lewy bodies. The correlation between predicted value and observed value is 0.9037924, lower than the correlation general model for all diagnosis groups, which is 0.9275027. Accordingly, the R-squared of semiparametric model for Lewy bodies group is 0.8168407, lower than that of the model for general population in training data, which is 0.8602612.

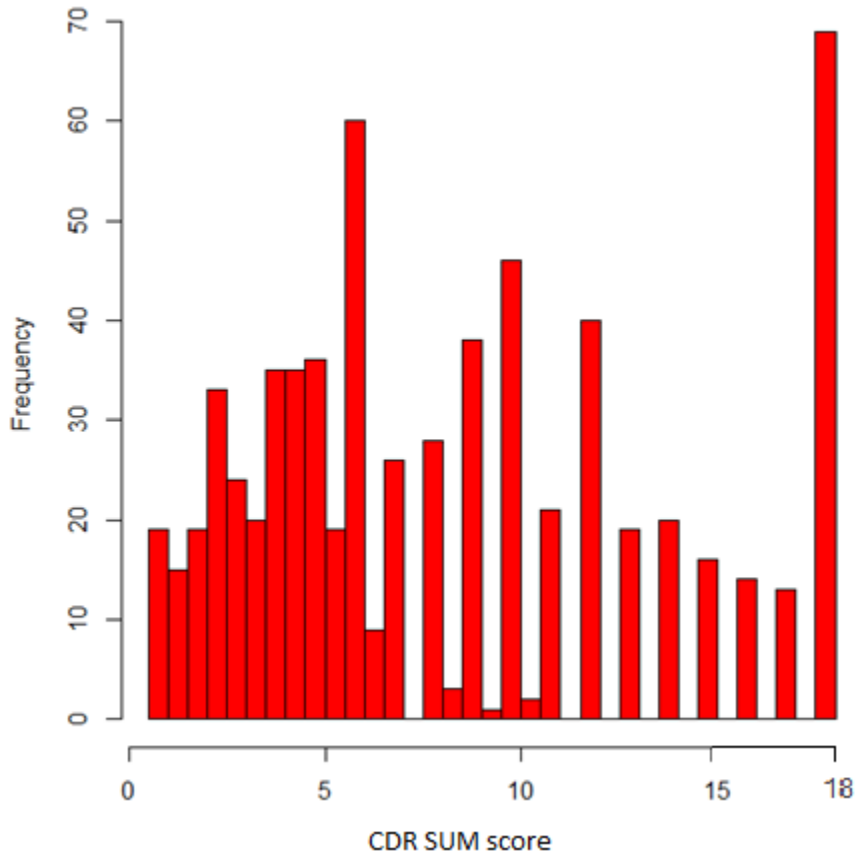

Figure 4.14. Histogram for observed CDR SUM values in Lewy bodies dementia
The x-axis represents actual CDRSUM value in training data, and y-axis is the frequency appeared.

The residual plot for predicted value as Figure 4.14 showed uniformity except for several outliers. The residual value is the observed value minus predicted value. Therefore, we can see that the predicted value has higher chances to to be overestimated than actual value. For

example, when CDR SUM score is 18, most of the predicted values are actually smaller than 18, the positive residual error is smaller than 5. However, because of the ceiling effect of CDR SUM score scale (maximum 18 points), the rest of the predictions are larger than 18, and we can avoid the prediction error by forcing the maximum prediction value as 18. As it is shown in Figure 4.15, the distribution of residual frequency resembles normal distribution, and this indicates that the prediction model for Lewy bodies dementia explains the data well.

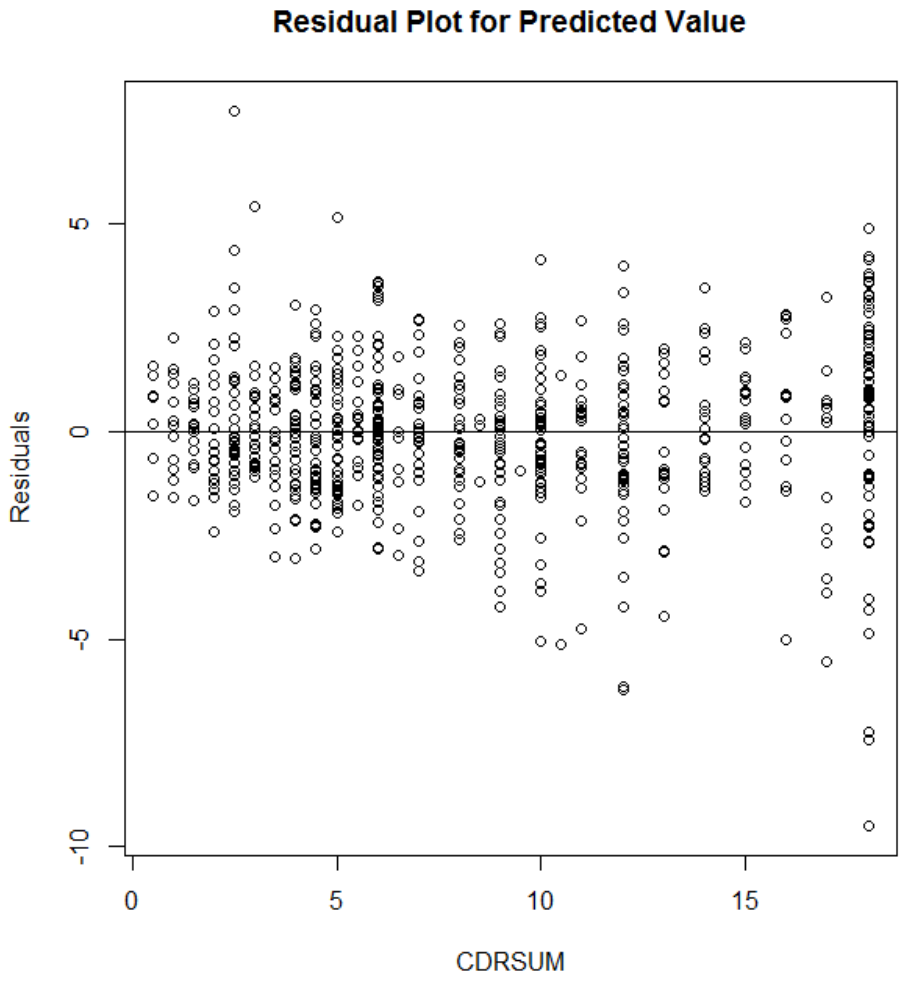

Figure 4.15. Residual plot for semiparametric model for Lewy bodies dementia
The x-axis represents actual CDRSUM value in training data, and y-axis is the value of residuals.

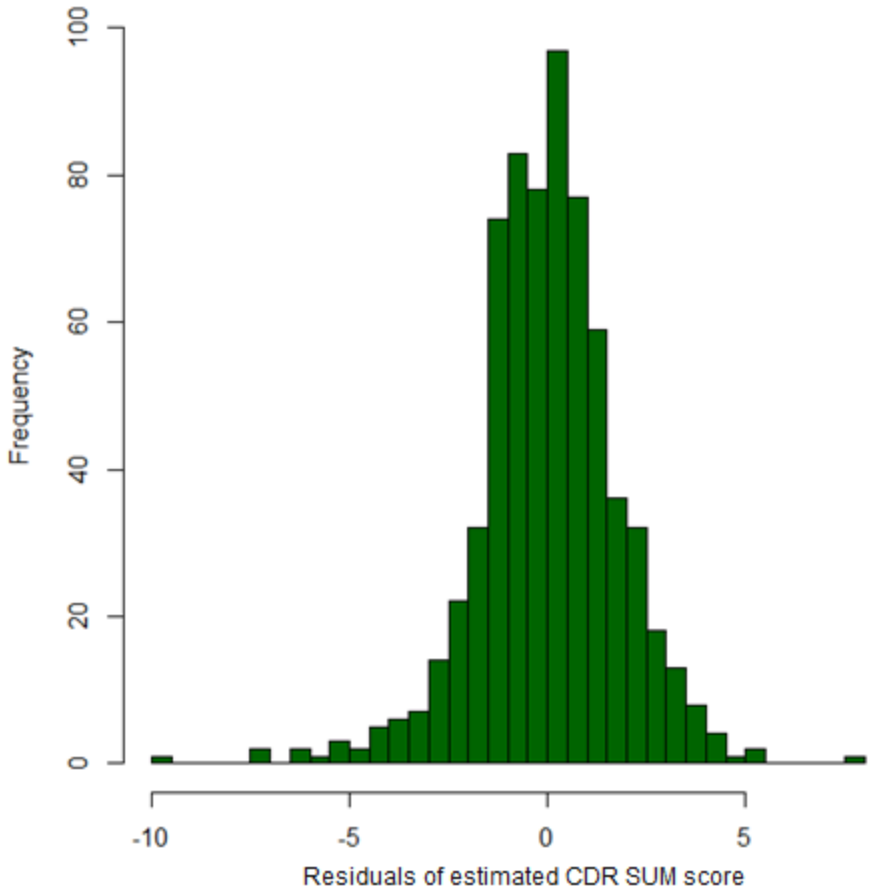

Figure 4.16. Histogram of residuals
The x-axis represents the value of residuals. The y-axis is the percentage of residual frequency.

From the perspective of training data fit, the model did well in fitting and explaining the training data. However, in order to generalize the model, validating the model by test data is essential. Again, bootstrap technique is used to generate random testing data among the alive patient records.

Table 4.12

Parameters of semiparametric model for Lewy bodies

	Value	Std.Error	t-value	p-value
(Intercept)	3.09	1.80	1.72	0.09
DURATION	0.04	0.44	0.09	0.93
I(DURATION^2)	0.08	0.02	3.37	0.00
AgeonsetOld	0.24	2.25	0.11	0.91
AgeonsetYoung	-0.21	0.99	-0.21	0.83
EduLevel>=12 years	-1.40	1.00	-1.40	0.16
SEX	-0.29	1.02	-0.28	0.78
CVHATT	0.37	0.21	1.77	0.08
CVAFIB	-0.02	0.25	-0.08	0.93
CBSTROKE	0.15	0.16	0.92	0.36
CBTIA	-0.26	0.17	-1.51	0.13
DIABETES	0.58	0.49	1.18	0.24
DEL	1.10	0.33	3.35	0.00
HALL	0.81	0.30	2.70	0.01
AGIT	0.76	0.32	2.34	0.02
DEPD	-0.46	0.29	-1.62	0.11
ANX	0.30	0.30	1.01	0.31
ELAT	-0.77	0.62	-1.25	0.21
APA	0.51	0.29	1.77	0.08
DISN	0.57	0.38	1.51	0.13
IRR	-0.01	0.32	-0.04	0.97
MOT	1.08	0.33	3.22	0.00
NITE	0.01	0.29	0.03	0.97
APP	0.23	0.28	0.81	0.42
DURATION:AgeonsetOld	-0.87	0.98	-0.89	0.38
DURATION:AgeonsetYoung	-0.15	0.24	-0.61	0.54
DURATION:SEX	0.49	0.27	1.80	0.07

By applying this model to the test data for Lewy bodies only, a simple linear function for observed CDR SUM score and predicted values can be created. The R-squared was 19.5% , indicating about 19.5% of the variance of observed CDR SUM score can be explained by predicted scores of the model (or vice-versa), which is a higher value than from the general model for all dementia types (17%). The correlation between predicted CDR SUM and observed CDR SUM was 0.44, 3% more than the correlation we got from the general model for all

dementia types (0.41). We assume that the true groupship of dementia type would contribute to the accuracy of the prediction results, and the improvement of model selection index are evidence of this assumption.

4. 7. Guideline for Model Application in Medical Practice

The CDR SUM score is a good indication for the cognitive deterioration level and has implications for the patient's performance on adjusting to his/her daily life independently.

O'Bryant et. al. (2008) proposed interpretive guidelines for CDR-SOB scores, which is the CDR SUM score in this study. It was stated that the guideline in O'Bryant et.al (2008) would further expand on the potential for increased precision in tracking change across time. The staging category is as Table 4.13 below:

Table 4.13

CDR SUM score staging category

CDR SUM score Range	Staging Category
0	Normal
0.5–4.0	Questionable cognitive impairment
0.5–2.5	*Questionable impairment*
3.0–4.0	*Very mild dementia(very early stage)*
4.5–9.0	Mild dementia (early stage)
9.5–15.5	Moderate dementia (middle stage)
16.0–18.0	Severe dementia (late stage)

Note: The table is adapted from the study by O'Bryant et al. (2008).

In normal stage (CDR SUM score-0), the subject are able to function day to day in the world, have normal judgment and are capable of taking care of their personal needs, and have a well maintained home and professional life.

In questionable impairment (CDR SUM score-(0.5-2.5)), there are one or several symptoms showing up: consistent slight forgetfulness, partial recollection events, some light difficulty with time relationships, slight impairment in solving problems, slight impairment in

job, shopping, volunteer and social groups, life at home, hobbies, and intellectual interests slightly impaired. Above all, these patients are fully capable of self-care, which means they can still maintain their own personal care without any support.

In very mild dementia stage (CDR SUM score-(3.0-4.0)). At least two domains have mild impairment. The symptoms in this stage include: moderate memory loss interferes with everyday activities, moderate difficulty with time relationships, unable to function independently at usual level in job, shopping, volunteer and social groups, mild but definite impairment of function at home; more difficult chores are abandoned, more complicated hobbies and interests are abandoned and prompting for personal care in dressing, bathing, eating and toileting is needed. However, social ability is usually maintained.

In mild dementia stage (CDR SUM score-(4.5-9.0)), there are noticeable impairments in each of the six key areas. Changes are still mild but issues with short-term memory will be noticeable and may affect some aspects of the patients' day. Individuals will start to become disorientated and may experience difficulty with directions or getting from one place to another. There may be some impact on their ability to care for themselves at home with chores and personal hygiene becoming neglected. Outside the home they may experience trouble in functioning independently.

In moderate dementia stage (CDR SUM score-(9.5-15.5)), patients experience severe memory loss, and only highly learned material are retained, new material are rapidly lost. There are more obvious signs of disorientation and difficulty in comprehending time and space. They remain well enough to take part in social activities but will now need to be accompanied. They will also need assistance with day to day activities and personal hygiene.

Severe dementia stage (CDR SUM score-(16.0-18.0)) is the most severe stage of dementia. Patients are no longer able to function without support. Extreme memory loss and very little or no understanding of time, place or geography occur. Full time help is required in the home to assist with personal care and they will no longer be able to engage in every day and social activities, even with assistance. Extra staffing and secure lock down areas for safety when wandering becomes a primary concern. Skilled care or nursing homes are needed for 24-hour supervision or skilled care provided by licensed nurses and other options are no longer feasible.

4. 8. Application as a Diagnosis Tool

To be a practical tool for prognosis or handy information for family of those who suffer from cognitive decline, a friendly and simple input interface would help to spread this trajectory estimation method. Although there is still more refinement can be done to make the prediction model can be refined to be more accurate and precise, we can still employ the model to obtain reference information about the progression of cognitive decline.

The future work needed include an application that has an interface that link BERT with Excel and R programming. The example interface can be referred to Table 4.14. The interface should include the patient's name, the information of age at onset, years of education, gender, the history of cardiac heart attack, transient ischemic attack/Atrial fibrillation, stroke, diabetes, and the information about neuropsychiatric symptoms (Delusion, Hallucination, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, night time behavior, and appetite change). This prediction application can be realized by BERT, which is a tool for connecting Excel with the statistics language R. It supports running R functions from Excel spreadsheet cells. The input of the form can be linked to spreadsheets and then processed in R, so that the prediction score can be obtained to give an estimation of a patient's cognitive decline trajectory.

Again, this tool is a reference for the trajectory of cognitive decline since some factors such as such as drug intake, life style, social network support, treatment, and quality of care received do potentially influent patient's cognitive performance. The predicted trajectory can be updated based on the latest profile upon each visit, since non serial correlation of CDR SUM score is supported by this study. The semiparametric model for the trajectory of cognitive decline is an empirical prediction tool that gives reliable and robust information on one's typical course of cognitive decline.

Table 4.14

Clinical dementia score estimation information input

Estimated duration since age at onset	( ) years
Gender	*1 (Male) 2 (Female)*
Years of Education	*">=12 years" (above high school education)* *"< 12 years" (below high school education)*
Age at onset	*"<=66 years old" ">66 and <=86 years old"* *">86 years old"*
Heart attack /Cardiac arrest	*0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)*
Transient ischemic attack	*0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)*
Atrial fibrillation	*0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)*
Stroke	*0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)*
Diabetes	*0 (Absent) 1 (Recent/Active) 2 (Remote/Inactive)*
Delusion	*0 (No) 1 (Yes)*
Hallucination	*0 (No) 1 (Yes)*
Agitation	*0 (No) 1 (Yes)*
Depression	*0 (No) 1 (Yes)*
Anxiety	*0 (No) 1 (Yes)*
Elation/euphoria	*0 (No) 1 (Yes)*
Apathy	*0 (No) 1 (Yes)*
Disinhibition	*0 (No) 1 (Yes)*
Irritability	*0 (No) 1 (Yes)*
Motor disturbance	*0 (No) 1 (Yes)*
Night time behavior	*0 (No) 1 (Yes)*
Appetite change in type of food	*0 (No) 1 (Yes)*

CHAPTER 5. CONCLUSION

Although millions of people are diagnosed as cognitive decline worldwide, there is still much misunderstanding about cognitive decline. It is not equal to dementia, and may leads to dementia. Dementia is a cognitive disorder that is associated with cognitive decline. It prevails in older populations and is difficult to make precise diagnosis. Before the diagnosis of dementia, there is an insidious stage that is defined as Mild Cognitive Decline. Cognitive decline is the impairment of the capacity to perform higher mental processes of reasoning, remembering, paying attention, understanding, and problem solving compared to one's normal performance. MCI is a condition in which an individual has mild but measurable changes in thinking abilities. The changes are noticeable to the person affected and to family members and friends, but do not affect the individual's ability to carry out everyday activities. This concept is rather heterogeneous with regard to its inclusion of a variety of types of cognitive dysfunction.

MCI does not always lead to dementia. Heterogeneity of MCI classifications result in different prevalence and conversion rates. In some individuals, MCI reverts to normal cognition or remains stable. The rate of progression of dementia is highly variable: some patients experience fast cognitive deterioration and have short survival time after cognitive decline onset. Some patients maintained constant cognitive level until death. Some patients have cognitive reversion back to normal and then impaired cognition again. This variability is a challenge for researchers to understand the pattern of dementia progression.

Patients and their families need to know what to expect with regards to cognitive decline behavior, severity of cognitive and functional decline and survival time. Therefore, determining models for simulating the trajectory of cognitive decline is critical given the heterogeneity.

We assume certain factors are associated with cognitive decline course and patients who share similar profiles would have similar decline trajectories. The CDR SUM score reflects the level that the cognitive decline affects a patient's standard of living, therefore, is a good indicator among many (such as MMSE) to study and make prediction. There were two goals in this study: first, to identify influential factors that can predict CDR SUM score. Second, to develop a robust trajectory model for predicting cognitive decline based on existing patient profiles.

The data in this study was collected as longitudinal data from Sep 2005 to Sep 2015, based on NACC database. Univariate analysis on interested factors were performed to identify the influential factors for CDR SUM score. Time is a primary factor studied in dementia progression. Although age is the strongest risk factor for dementia, we used duration and age at onset together to represent the effects of time. Based on the conclusion of past studies, we examined gender, years of education, vascular health conditions, and existence of neuropsychiatric symptoms. We justified the reasons not including APOE ε4 and diagnosis types. Linear regression, polynomial regression (with and without correlation), multilevel model and semiparametric models (with and without correlation) were applied in this study to fit the trajectory model.

We evaluated AIC and BIC values among the linear model, polynomial models, and polynomial model with series correlation models. Furthermore, we used R-squared and correlation between observed CDR SUM scores and predicted values to evaluate multilevel and semiparametric models. The semiparametric model without correlation had higher R-squared and correlation between observed CDR SUM scores and predicted values.

The findings from semiparametric mixed effect model provided more accurate information about the course of cognitive decline. Figure 5.1 is the effect of the influential

factors for predicting CDR SUM score. Since there is no correlation assumed for the same subject, the CDR SUM score can be estimated independently regardless of the value of previous CDR SUM score records. Neuropsychiatric symptoms including delusion, hallucination, agitation, anxiety, apathy, disinhibition, motor disturbance, and appetite change (eating change in type of food) were all indicators of higher CDR SUM scores. History of stroke presence and night time behavior (awakening during the night, rising too early or taking excessive naps during daytime) had smaller impacts on increasing CDR SUM scores. Furthermore, along with time, female gender showed higher CDR SUM score than their male counterparts. This could be the result of longer survival time for females.

Older age at onset (>86 years old), more than high school education (>=12 education years), and presence of irritation were all indicators that bring down the CDR SUM score. Education level was the most influential factor among these three indicators. Depression had minimal negative effect on CDRSUM score. This could be due to shorter survival time for patients with depression.

Among the factors we tested in SME(N-cor) model, there is little evidence that young age at onset (≤66 years old), sex, heart attak/cardiac arrest, atrial fibrillation, transient ischemic attack, diabetes, presence of elation, the interaction between duration and age at onset, and the interaction between duration and education level are significant ($p>0.05$). The performance of the model would decrease 50% if categorical factors of APOE ε4 were added into the model while the goodness of fit would still remain the same. This could be because the distribution of APOE ε4 alleles in the training data are not consistent with in the population and caused overfitting of the model. However, there were certain patterns of CDRSUM score associated with APOE genotype in the training data.

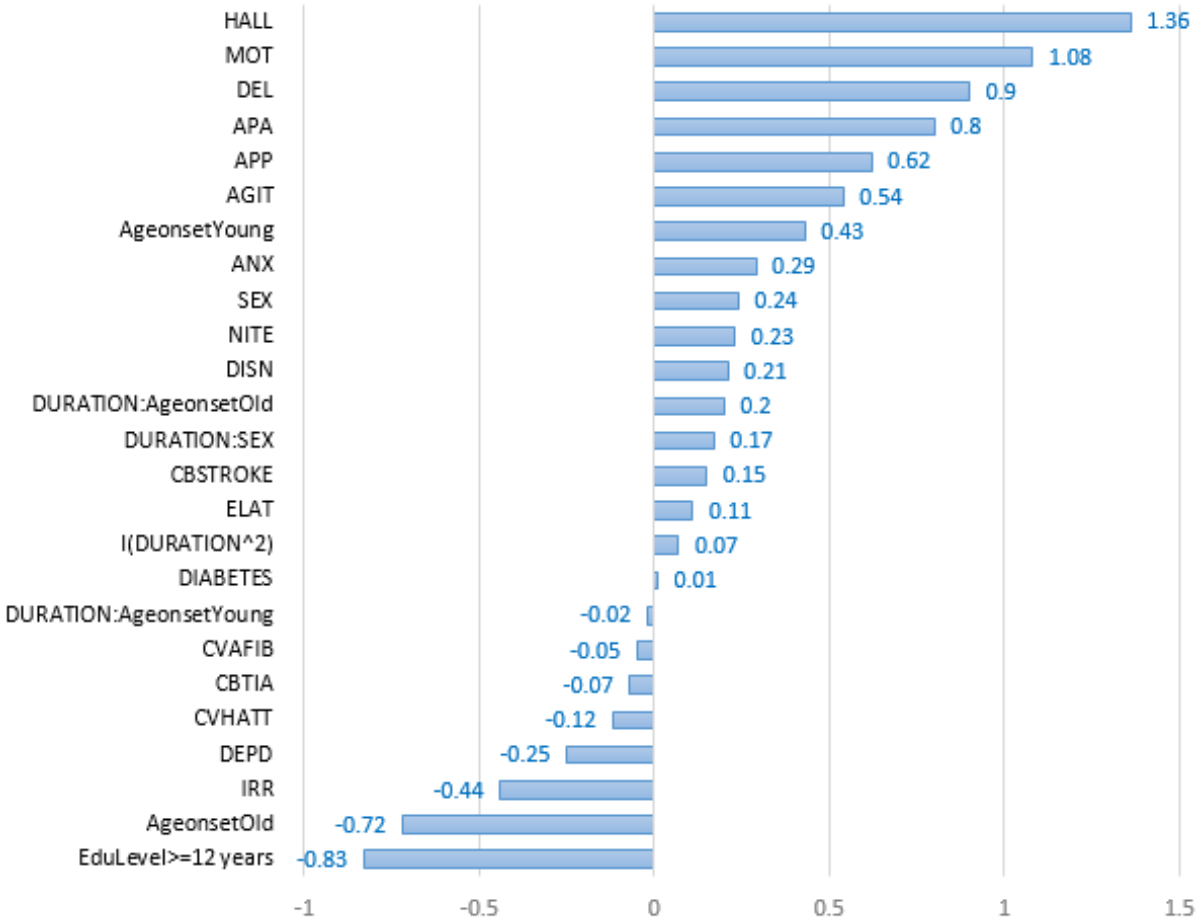

Figure 5.1. The effect of each influential factor in SME (N-cor) model

Panelized spline allows curve in the shape of the CDR SUM trajectory. Instead of linear growth, the model depicts slow cognitive decline in the early four years after onset, followed by a stable stage for four more years, and then a rapid decline thereafter. Generally, the trajectory shows an upward trend of CDRSUM score, which is typical in non-reversible dementia.

Several limitations of this study need to be kept in mind when interpreting the results. First, the samples were recruited based on clinic visits. This will have sampling bias compared to population-based study. Because it could be more likely that these subjects are living with family or friends, have more educational/professional attainment, or they have more awareness of cognition impairment. Second, samples were selected from those who had at least two

consecutive visits, i.e. two years' follow up. Those who had acute incident cognitive decline and dropped out/deceased in one year were not included in model building. This could lead to an overestimate of CDR SUM scores due to overestimated survival time. Third, the samples were selected from American Caucasians due to the sample collection geographic features; therefore, the implication of the results should be carefully restricted to this specific race. Fourth, our study did not include some potentially important factors' impact on the progression, such as drug intake, lifestyle, social network support, treatment, and quality of care received, therefore, the overall individual case is important in CDR SUM score prediction and should be considered as supplementary information in prediction. Fifth, because the reversion of cognitive/functional ability is possible (Koepsell & Monsell, 2012), a sub model would be better to represent the trajectory for people who have reversion. Finally, since pathological evidence from biopsy study showed that rate of cognitive and functional decline for subjects with Mixed AD and vascular and Mixed AD and Lewy Body pathology was slower in CDR scores (Pillai et al., 2015), it would be better to classify patients when high diagnosis accuracy can be reached with technique advance.

In spite of the limitations above, this study proposed several models to estimate the progression trajectory of cognitive decline in dementia. The innovative application of semiparametric mixed effect model provides implication on estimation in longitudinal studies, and this method can also be applied to other chronic disease studies that can help make prognosis and measure effectiveness of various kinds of medical trials.

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APPENDIX A. CAUSE AND CHARACTERISTICS OF MAJOR TYPES OF DEMENTIA

Cause	Characteristics
Alzheimer's disease	Most common; accounts for an estimated 60 percent to 80 percent of cases. About half of these cases involve solely Alzheimer's pathology; many have evidence of pathologic changes related to other dementias. This is called mixed dementia (see mixed dementia in this table). The hallmark pathologies of Alzheimer's are the progressive accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. These changes are eventually accompanied by the damage and death of neurons.
Vascular dementia	Previously known as multi- or post-stroke dementia, accounting for about 10 percent of dementia cases. It is very common in older individuals with dementia, with about 50 percent having pathologic evidence of vascular dementia (infarcts). Vascular dementia occurs most commonly from blood vessel blockage or damage leading to infarcts (strokes) or bleeding in the brain. The location, number and size of the brain injuries determine whether dementia will result and how the individual's thinking and physical functioning will be affected.
Dementia with Lewy bodies (DLB)	People with DLB have some of the symptoms common in Alzheimer's, but are more likely to have initial or early symptoms of sleep disturbances, well-formed visual hallucinations and slowness, gait imbalance or other parkinsonian movement features. These features, as well as early visuospatial impairment, may occur in the absence of significant memory impairment. DLB is a disease associated with abnormal deposits of a protein called alpha-synuclein in the brain. These deposits, called **Lewy bodies**, affect chemicals in the brain whose changes, in turn, can lead to problems with thinking, movement, behavior, and mood. When they develop in a part of the brain called the cortex, dementia can result.
Frontotemporal lobar degeneration (FTLD)	Includes dementias such as behavioral-variant FTLD, primary progressive aphasia, Pick's disease, corticobasal degeneration and progressive supranuclear palsy. Typical early symptoms include marked changes in personality and behavior and difficulty with producing or comprehending language. Unlike Alzheimer's, memory is typically spared in the early stages of disease. Nerve cells in the front (frontal lobe) and side regions (temporal lobes) of the brain are especially affected, and these regions become markedly atrophied (shrunken). In addition, the upper layers of the cortex typically become soft and spongy and have protein inclusions (usually tau protein or the transactive response DNA-binding protein)

Cause	Characteristics
Parkinson's disease (PD) dementia	Problems with movement (slowness, rigidity, tremor and changes in gait) are common symptoms of PD. In PD, alpha-synuclein aggregates appear in an area deep in the brain called the substantia nigra. The aggregates are thought to cause degeneration of the nerve cells that produce dopamine. The incidence of PD is about one-tenth that of Alzheimer's.
prion disease	This prion disease is similar to mad cow disease that has been found in wild deer, elk and moose. This very rare and rapidly fatal disorder impairs memory and coordination and causes behavior changes. Results from a misfolded protein (prion) that causes other proteins throughout the brain to misfold and malfunction. May be hereditary (caused by a gene that runs in one's family), sporadic (unknown cause) or caused by a known prion infection. A specific form called variant Creutzfeldt-Jakob disease is believed to be caused by consumption of products from cattle affected by mad cow disease.
Normal pressure hydrocephalus	Caused by impaired reabsorption of cerebrospinal fluid and the consequent build-up of fluid in the brain, increasing pressure in the brain. Symptoms include difficulty walking, memory loss and inability to control urination. Accounts for less than 5 percent of dementia cases.

Adapted from 2015 Alzheimer's disease Facts and Figures. The Original report is available at https://www.alz.org/facts/downloads/facts_figures_2015.pdf. *Copyright permission obtained from the Alzheimer's Association Copyright Department on Mar 22, 2017.*

APPENDIX B. CLINICAL DEMENTIA RATING SCORE

See the following page.

Subject Initials _____

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3
	None 0	Questionable 0.5	Impairment Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

APPENDIX C. DERIVATION OF BAYESIAN INFORMATION CRITERION

True or generating model: $g(y)$

Candidate or approximating model: $f(y|\theta_k)$

Candidate class:

$$\mathrm{F}(k) = \{f(y|\theta_k)|\theta_k \in \Theta\ (k)\}$$

Fitted model: $f(y|\hat{\theta}_k)$

Let *y* denote the observed data.

Assume that y is to be described using a model $\boldsymbol{M_k}$ selected from a set of candidate models $\boldsymbol{M_{k1}}, \boldsymbol{M_{k2}}, \ldots, \boldsymbol{M_{kL}}$.

Assume that each $\boldsymbol{M_k}$ is uniquely parameterized by a vector θ_k , where θ_k is an element of the parameter space $\Theta\ (k)$ (k$\in \{k_1, k_2, \ldots, k_L\}$).

Let $L(\theta_k|y)$ denote the likelihood for *y* based on $\boldsymbol{M_k}$. $L(\theta_k|y)$ =f $(y|\theta_k)$

Let $\hat{\theta}_k$ denote the maximum likelihood estimate of $\hat{\theta}_k$ obtained by maximizing $L(\theta_k|y)$ over $\Theta\ (k)$.

We assume that derivatives of $L(\theta_k|y)$ up to order two exist with respect to k , and are continuous and suitably bounded for all $\theta_k \in \Theta\ (k)$.

The motivation behind BIC can be seen through a Bayesian development of the model selection problem.

Let $\pi(k)$ (k $\in \{k_1, k_2, \ldots, k_L\}$)denote a discrete prior over the models $\boldsymbol{M_{k1}}, \boldsymbol{M_{k2}}, \ldots, \boldsymbol{M_{kL}}$.

Let $g(\theta_k|k)$ denote a prior on θ_k given the model $\boldsymbol{M_k}$ (k $\in \{k_1, k_2, \ldots, k_L\}$).

Applying Bayes' Theorem, the joint posterior of $\boldsymbol{M_k}$ and θ_k can be written as

$$h\big((k, \theta_k)\big|y\big) = \frac{\pi(k)g(\theta_k|k)L(\theta_k|y)}{m(y)}$$

where $m(y)$ denotes the marginal distribution of *y*.

A Bayesian model selection rule might aim to choose the model $\boldsymbol{M_k}$ which is a posteriori most probable.

$$P(k|y) = m(y)^{-1}\pi(k) \int L(\theta_k|y)\ g(\theta_k|k)d\theta_k$$

$$lnP(k|y) = -ln\{m(y)\} + ln\{\pi(k)\} + ln\{\int L(\theta_k|y)\ g(\theta_k|k)d\theta_k\}$$

We take a second-order Taylor series expansion of the log-likelihood about $\hat{\theta}_k$

$$lnL(\theta_k|y) \approx lnL\big(\hat{\theta}_k\big|y\big) + (\theta_k - \hat{\theta}_k)' \frac{\partial lnL(\hat{\theta}_k|y)}{\partial \theta_k} + \frac{1}{2}(\theta_k - \hat{\theta}_k)' \left[\frac{\partial^2 lnL(\hat{\theta}_k|y)}{\partial \theta_k \partial \theta_k'}\right](\theta_k - \hat{\theta}_k)$$

$$= lnL\big(\hat{\theta}_k\big|y\big) - \frac{1}{2}(\theta_k - \hat{\theta}_k)'\big[n\bar{\mathcal{I}}\ (\hat{\theta}_k, y)\big](\theta_k - \hat{\theta}_k)$$

$\bar{\mathcal{I}}\ \big(\hat{\theta}_k, y\big) = -\frac{1}{n}\ \frac{\partial^2 lnL(\hat{\theta}_k|y)}{\partial \theta_k \partial \theta_k'}$ is the Average observed Fisher information matrix

$$L(\theta_k|y) \approx L\big(\hat{\theta}_k\big|y\big) exp\{-\frac{1}{2}(\theta_k - \hat{\theta}_k)'\big[n\bar{\mathcal{I}}\ (\hat{\theta}_k, y)\big](\theta_k - \hat{\theta}_k)\}$$

$$\int L(\theta_k|y)\ g(\theta_k|k)d\theta_k \approx L\big(\hat{\theta}_k\big|y\big) \int exp\{-\frac{1}{2}(\theta_k - \hat{\theta}_k)'\big[n\bar{\mathcal{I}}\ (\hat{\theta}_k, y)\big](\theta_k - \hat{\theta}_k)\}\, g(\theta_k|k)d\theta_k$$

Using the noninformative prior $g(\theta_k|k) = 1$

$$\int exp\{-\frac{1}{2}(\theta_k - \hat{\theta}_k)'\big[n\bar{\mathcal{I}}\ (\hat{\theta}_k, y)\big](\theta_k - \hat{\theta}_k)\}\, g(\theta_k|k)d\theta_k = (2\pi)^{(k/2)}\big|n\bar{\mathcal{I}}\ (\hat{\theta}_k, y)\big|^{-1/2}$$

$$\int L(\theta_k|y)\ g(\theta_k|k)d\theta_k \approx L\big(\hat{\theta}_k\big|y\big)\ (2\pi)^{(k/2)}\big|n\bar{\mathcal{I}}\ \big(\hat{\theta}_k, y\big)\big|^{-\frac{1}{2}}$$

$$= L\big(\hat{\theta}_k\big|y\big)\ (2\pi)^{(k/2)} n^{(-k/2)}\big|\bar{\mathcal{I}}\ \big(\hat{\theta}_k, y\big)\big|^{-\frac{1}{2}}$$

$$= L\big(\hat{\theta}_k\big|y\big)\ \big(2\pi/n\big)^{(k/2)}\big|\bar{\mathcal{I}}\ \big(\hat{\theta}_k, y\big)\big|^{-\frac{1}{2}}$$

Let $S(k|y) \equiv -2lnP(k|y)$

$$-2lnP(k|y) \propto -2\, ln\{\pi(k)\} - 2ln\{\int L(\theta_k|y)\ g(\theta_k|k)d\theta_k\}$$

Now consider minimizing $-2lnP(k|y)$as opposed to maximizing $P(k|y)$.

We have

$$-2lnP(k|y) = 2\,ln\{m(y)\} - 2\,ln\{\pi(k)\} - 2ln\{\int L(\theta_k|y)\;\; g(\theta_k|k)d\theta_k\}$$

The term involving $m(y)$ is constant with respect to k; thus, for the purpose of model selection, this term can be discarded.

We can now write

$$S(k|y) = -2\,ln\{\pi(k)\} - 2ln\{\int L(\theta_k|y)\;\; g(\theta_k|k)d\theta_k\}$$

$$\approx -2\,ln\{\pi(k)\} - 2[L\left(\hat{\theta}_k|y\right)\left(2\pi/n\right)^{(k/2)}\left|\bar{I}\left(\hat{\theta}_k\,,y\right)\right|^{-\frac{1}{2}}]$$

$$= -2\,ln\{\pi(k)\} - 2lnL\left(\hat{\theta}_k|y\right) + k\{ln(n/2\pi)\} + ln\left|\bar{I}\left(\hat{\theta}_k\,,y\right)\right|$$

Assume sample size n grows to infinity, we can ignore the terms in the preceding that are bounded.

$$S(k|y) \approx -2lnL\left(\hat{\theta}_k|y\right) + kln(n)$$

Minimizing $S(k|y)$, we define Bayesian(Schwarz) information criterion (BIC) as:

$$\text{BIC} = -2lnL\left(\hat{\theta}_k|y\right) + kln(n)$$

APPENDIX D. DESCRIPTION OF NEUROPSYCHIATRIC SYMPTOMS

1. *Delusions.* The patient believes that others are planning to harm him or her in some way. He/she believes that others are stealing from him or her. He/she says that family members are not who they say they are or that the spouse is being unfaithful. The patient is not only suspicious, but also convinced these things are happening.
2. *Hallucinations.* The patient acts as if he/she hears voices. He/she talks to people who are not there. He/she seems to see, hear or experience things that are not present. (This behavior is different from that of believing that a long-dead person is still alive.)
3. *Agitation/Aggression.* The patient has periods of verbal or physical agitation or aggression. Behaviors include screaming, temper outbursts, swearing, repeated calling out, pushing, biting, hitting, scratching, grabbing, throwing objects, spitting, kicking, wandering, pacing, elopement, intrusion into others' rooms, inappropriate voiding. The patient has periods of refusing to cooperate or being resistant to help from others. The patient is hard to handle.
4. *Depression/Dysphoria*. The patient seems sad or in low spirits. He/she says that he/she feels* sad or depressed. He or she cries.

   * Dysphoria: Mood disturbance associated with anxiety.
5. *Anxiety.* The patient is very nervous, worried, or frightened for no apparent reason. He/she is very tense or fidgety. The patient becomes upset when separated from an object or person who offers comfort.
6. *Apathy/Indifference.* The patient seems less interested in the world around and in enjoyable daily activities. He/she lacks motivation for starting new activities. He/she is more difficult to engage in conversation.

7. *Irritability/Lability.* The patient gets irritated and easily disturbed. His/her moods are very changeable. He/she is abnormally impatient and cranky.

8. *Elation/Euphoria.* The patient has a persistent and abnormally good mood (i.e. he/she feels too cheerful or acts excessively happy) for no reason.

9. *Disinhibition.* The patient acts impulsively. He/she does or says things that are not usually done or said in public which are embarrassing to people, or that may hurt people's feelings. The patient may talk to strangers as if he or she knows them. Inappropriate disrobing or sexual behavior are also examples of disinhibition.

10. *Aberrant motor behavior.* The patient engages in repetitive activities such as pacing, or does things repeatedly such as opening closets or drawers. The patient may constantly pick at clothes or skin, tap fingers, jiggle a leg, or rub an object, (for example, "polishing" a piece of furniture.)

11. *Sleep.* The patient has difficulty sleeping. He /she wanders at night, gets dressed, awakens during the night, rises too early in the morning, takes excessive naps during the day.

12. *Appetite and eating disorders.* He/she has had a change in appetite or eating habits. (Rate N/A if the patient cannot feed himself). The patient has lost or gained significant weight.

(Resource: NACC Uniform Data Set Coding Guidebook, Form B5: Behaviroal Assessment-Neuropsychiatric Inventory Questionnaire (NPI-Q)