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MODELING DEMENTIA RISK, COGNITIVE CHANGE, PREDICTIVE RULES IN LONGITUDINAL STUDIES

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MODELING DEMENTIA RISK, COGNITIVE CHANGE, PREDICTIVE RULES IN LONGITUDINAL STUDIES

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Public Health
at the University of Kentucky

By
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Lexington, Kentucky

2016

ABSTRACT OF DISSERTATION

MODELING DEMENTIA RISK, CONGNITIVE CHANGE, AND PREDICTIVE MODELING IN LOGITUDINAL STUDIES

Dementia is increasing recognized as a major problem to public health worldwide. Prevention and treatment strategies are in critical need. Nowadays, research for dementia usually featured as complex longitudinal studies, which provide extensive information and also propose challenge to statistical methodology. The purpose of this dissertation research was to apply statistical methodology in the field of dementia to strengthen the understanding of dementia from three perspectives: 1) Application of statistical methodology to investigate the association between potential risk factors and incident dementia. 2) Application of statistical methodology to analyze changes over time, or trajectory, in cognitive tests and symptoms. 3) Application of statistical learning methods to predict development of dementia in the future.

Prevention of Alzheimer's disease with Vitamin E and Selenium (PREADViSE) (7547 subjects included) and Alzheimer's disease Neuroimaging Initiative (ADNI) (591 participants included) were used in this dissertation. The first study, "Self-reported sleep apnea and dementia risk: Findings from the PREADViSE Alzheimer's disease prevention trial ", shows that self-reported baseline history of sleep apnea was borderline significantly associated with risk of dementia after adjustment for confounding. Stratified analysis by *APOE* ε4 carrier status showed that baseline history of sleep apnea was associated with significantly increased risk of dementia in *APOE* ε4 non-carriers. The second study, "comparison of trajectories of episodic memory for over 10 years between baseline normal and MCI ADNI subjects," shows that estimated 30% normal subjects at baseline assigned to group 3 and 6 stay stable for over 9 years, and normal subjects at baseline assigned to Group 1 (18.18%) and Group 5 (16.67%) were more likely to develop into dementia. In contrast to groups identified for normal subjects, all trajectory groups for MCI subjects at baseline showed the tendency to decline. The third study, "comparison between neural network and logistic regression in PREADViSE trial," demonstrates that neural network has slightly better predictive performance than logistic

regression, and also it can reveal complex relationships among covariates. In third study, the effect of years of education on response variable depends on years of age, status of *APOE* ε4 allele and memory change.

KEYWORDS: longitudinal analysis, dementia, group based trajectory modeling, neural network

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July 13, 2015
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MODELING DEMENTIA RISK, CONGNITIVE CHANGE, AND PREDICTIVE MODELING IN LOGITUDINAL STUDIES

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Date

To Yongchao, Eric, my parents Keqin Ding, Huanlian Sun

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TABLE OF CONTENTS

Acknowledgements…….. iii

List of Tables……... v

List of Figures…….. vi

Chapter One: Introduction……... 1

Chapter Two: Self-reported sleep apnea and dementia risk: Findings from the PREADViSE Alzheimer's disease prevention trial
- Abstract…… 7
- Introduction…….. 8
- Methods…… 10
- Results…….. 14
- Discussion…… 15

Chapter Three: Comparison of trajectories of episodic memory for over 10 years between baseline normal and MCI ADNI subjects
- Abstract…… 27
- Introduction……. 28
- Methods…… 29
- Results…….. 34
- Discussion…… 37

Chapter Four: Comparison between neural network and logistic regression in PREADViSE trial
- Abstract…… 48
- Introduction…….. 49
- Methods…… 50
- Results……. 57
- Discussion…… 60

Chapter Five: Conclusion
- Summary……. 70
- Strengths and Limitations……... 73
- Future Research…….. 74

Appendices……..... 76

References…….. 79

Vita……. 91

LIST OF TABLES

Table 2.1, General Characteristics of the Study Population in PREADViSE …….. 21

Table 2.2, Association between History of Sleep Apnea and Risk Dementia based on Adjusted Cox Model and Stratified Analysis by APOE ε4 Status …….. 22

Table 3.1, Subject characteristics for ADNI1 participants and by cognitive status.. 42

Table 3.2, Description of identified groups from the trajectory modeling ……... 43

Table 3.3, Characteristics of the subjects in each trajectory group……... 44

Table 3.4, Parameter estimate for risk factors associated with each trajectory group……..……..... 45

Table 4.1, General Characteristics of participants in PREADViSE ……..... 64

Table 4.2, Illustration effect of education by age, APOE-ε4 allele and memory change status for hypothetical subjects from neural network ……..... 65

Table 4.3. Parameter estimates from interaction of logistic regression……..... 66

Table 4.4, Estimated probability of having dementia from multivariable logistic regression to illustrate interaction effects among age at baseline, education, APOE- ε4 allele and memory change ……. 67

Table 4.5, Comparison of predictive performance of logistic regression and neural network.……. 68

LIST OF FIGURES

Figure 2.1, Participant flow diagram for PREADViSE..... 23

Figure 2.2. Probability of dementia by history of sleep apnea (SDB) at baseline. Solid line indicates sleep apnea, dashed line indicates no sleep apnea. Time axis ends at 10 years for consistency among figures..... 24

Figure 2.3. Probability of dementia at baseline by history of sleep apnea (SDB) status after adjusting other covariates in *APOE* ε4 non-carriers (a) and carriers (b). 25

Figure 3.1. Model based trajectories identified for baseline normal ADNI participants..... 46

Figure 3.2. Model based trajectories identified for baseline MCI ADNI participants. 47

Figure 4.1. Graphics of neural network for incidence of dementia in PREADVISE trial. 69

CHAPTER ONE

Introduction

Dementia is not a disease but a term that describes a group of symptoms[1]. It indicates a loss of cognitive functioning, such as the loss of the ability to think, remember, and reason, as well as behavioral abilities, and it interferes with a person's daily life and activities[2]. As the world's population ages, the prevalence of dementia rises. Prevalence of AD is currently estimated at 5.4 million cases in the United States, and the Alzheimer's Association reports that by 2050 that an estimated 16 million Americans will have AD. Researchers estimate that dementia will become the most expensive chronic condition associated with aging [3, 4]. Given current costs associated with the care and treatment of AD, in 2050 the annual cost of AD will reach 1.1 trillion dollars[5].

Many neurological diseases can present as a dementia, but the most common cause is Alzheimer's disease (AD), which accounts for 60 to 80 percent of dementia cases[1]. Clinically AD usually occurs after age 65. It is characterized clinically by deficits in memory and thinking, combined with impaired activities of daily living (ADLs)[6]. Pathologically AD is defined as the presence of beta-amyloid (i.e., neuritic plaques) and tau (i.e., neurofibrillary tangles) pathology, which only can be determined at the time of autopsy[7].

In epidemiological studies, researchers often describe a subject's cognitive status as normal, mild cognitive impairment (MCI), or dementia. The term MCI first appeared in the Global Deterioration Scale and was described as the earliest clear-cut cognitive deficits[8]. MCI was often defined as noticeable deficits in memory without

significant impact on daily functioning[9] . Clinical diagnosis of MCI is based on evaluation of medical history, assessment of independent function and daily activities with input from family members or friends. There are no tests or procedures to conclusively diagnose MCI. Patients diagnosed with MCI have increased risk to progress to dementia [10], but they also can remain at the MCI stage until death, and some of them revert to a normal cognitive state[11, 12].

In longitudinal studies of aging and dementia, healthy subjects without dementia and other neurological and/or neuropsychiatric conditions are usually recruited and evaluated for cognitive function and functional abilities at baseline and, then followed up annually for their cognitive status. Annual tests of cognition typically include multiple cognitive instruments, often collected over multiple decades. Appropriate and powerful statistical methods are important to analyze these complex data. In this project, application of statistical methodology in the field of dementia will be discussed and then performed to strengthen the understanding of dementia from three perspectives: 1) Application of statistical methodology to investigate the association between potential risk factors and incident dementia. 2) Application of statistical methodology to analyze changes over time, or trajectory, in cognitive tests and symptoms. 3) Application of statistical learning methods to predict development of dementia in the future.

Application of statistical methods in association between risk factors and incident dementia.

Multivariable logistic regression [13-16] and the proportional hazards model [17-22] are commonly used methods to study risk factors associated with incidence of dementia or related binary outcomes based on various research questions. In the proportional

hazards model, time to incident dementia is recorded for individuals and hazard ratios and time to event are estimated for groups. Logistic regression is most often used in fixed-period follow-up longitudinal studies, which means that subjects are followed up for the same amount of time, and cognitive status is assessed at the end of the study. Depending on the research questions and study design, different covariates are often incorporated into the statistical model. Some studies have applied multi-state models [23, 24] to accommodate various research interests regarding risk factors.

Application of statistical methods in cognitive trajectories or changes over time of cognition test or symptom

Various statistical methods have been developed and applied to describe change in outcomes for cognitive measurements over time and the association between change with risk factors, including but not limited to linear mixed effect model (LMM), mixed membership trajectory model (MMTM)[25], latent change score modeling[26], multi-stage disease progression model[27], Markov processes[28], mixed-effects beta regression[29], boundary inflated beta regression and coarsening model, tract based spatial statistics[30], and latent profile approach[31].

LMM is used generally for describing changes in continuous outcomes overtime [32-34]. One appealing aspect of LMM is that it is very flexible in accommodating any degree of imbalance in longitudinal data, which means it does not require the same number of observations on each subject nor that the measurements be taken at the same occasions.

However, LMM depends on several assumptions: (1) outcome of interest is continuous; (2) random components of the model are normally distributed; (3) assuming

no interaction among the covariates, a one unit change in any predictor is estimated to have a constant linear effect on mean level of outcome [35]. There have been some arguments about the use of LMM in aging studies [35-37]**.** For example, cognitive tests are usually discrete quantitative outcomes with a limited range of possible values and, they can suffer from ceiling and/or floor effects. [35, 37] Further, they usually do not change linearly over time.

Nagin and colleagues developed a longitudinal statistical approach – group based trajectory model (GBTM) that can copy the problems noted above. It can accommodate the discrete nature and truncated distribution of the outcome. It assumes that the sample is composed of a mixture of distinct groups, and that each group of individuals follows a similar developmental trajectory in terms of changes at mean level of outcome measurements [38-41]. Furthermore, one advantage of GBTM is that it qualitatively identifies distinct developmental groups that may not be identifiable by using LMM [42, 43]. Another advantage is that the model can distinguish real differences from chance variation. GBTM has been applied in prior cognitive studies. For example, Xie et al. applied GBTM to identify and characterize 5 trajectories of cognitive change in MCI subjects using the Mini-Mental State Examination (MMSE) [44]. Their results demonstrated heterogeneity of trajectories in MCI patients and that over half of MCI subjects follow a stable trajectory over time.

Application of statistical learning methods to predict development of dementia

Early identification of individuals with high risk of dementia is of great importance to prevent or delay dementia onset if prevention therapies emerge in the future. Two systematic reviews have covered nearly all parametric research methods

used for prediction of dementia risk in the past decades [45, 46]. These prediction models were mostly developed from logistic regression [47-50] or proportional hazards regression analysis [51-56] , and final models were selected based on p values or Bayesian Information Criterion. Performance of these models was assesses for discriminative accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and internal calibration. C-statistics reported from these models ranged from 0.49 to 0.89[48, 57]. Cut-off points were only reported in a few studies [47, 55, 58], but none of them had both sensitivity and specificity over 80%. These two comprehensive reviews concluded that none of the methods are recommended for dementia risk prediction in the population setting due to sample selection, model diagnostics, and model validation [45, 46]. Only four models covered in the two research reviews performed model validation issues [52, 54, 57, 59]. From a non-parametric model perspective, the classification tree is the most often used method [60, 61]. There are also other statistical learning methods such as random forest[62], neural network[63].

The purpose of this study is to assess risk factors and modelling strategies in longitudinal studies of aging and cognition. The specific aims of this study are:

Chapter 2: Investigate the association between sleep apnea and risk of dementia in the 11-year Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE) trial and whether the association depends on the status of the unmodifiable genetic risk factor APOE4.

Chapter 3: Explore potential trajectories in episodic memory scores in normal and MCI subjects enrolled in the Alzheimer's disease Neuroimaging Initiative (ADNI) cohort and assess whether these trajectories differ by cognitive status.

Chapter 4: Apply parametric and nonparametric statistical learning methods to create a prediction rule for predicting the development of dementia in the PREADViSE study.

CHAPTER TWO

Self-reported sleep apnea and dementia risk: Findings from the PREADViSE Alzheimer's disease prevention trial

Abstract

Sleep apnea is a common condition and has a direct impact on cognitive function. The impact of sleep apnea, and its interplay with other established risk factors, on the risk of incident dementia warrants exploration.To investigate the association between baseline sleep apnea and risk of incident dementia in the Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADViSE) study and explore whether the association depends on APOE ε4 allele status, randomized controlled dementia prevention trial followed by exposure study with over 11 years of follow up was used. Participants were assessed at 128 local clinical study sites during the clinical trial phase and later were followed by telephone from a centralized location.7,547 male subjects were enrolled in PREADViSE, and 4,271 of them consented to participate in the exposure study. Participants were interviewed at baseline for sleep apnea. The Memory Impairment Screen (MIS) was administered to each participant annually. Subjects who failed to this initial screen were tested with secondary cognitive screening tests. Additional measures collected include medical history, medication use, and the AD8 dementia screening instrument. The effect of self-reported sleep apnea on dementia risk depends on APOE ε4 status. When the allele was absent, baseline self-reported sleep apnea was associated with a 66% higher risk of developing dementia (95% CI 2%-170%), while self-reported sleep apnea conferred no additional risk for participants with an ε4 allele. Sleep apnea may increase risk of dementia in the absence of APOE-ε. This may help inform prevention strategies for dementia or AD in older men with sleep apnea.

Introduction

Dementia is a syndrome that affects memory, thinking, behavior and ability to perform everyday activities. In 2010, Mimo and colleagues estimated global dementia prevalence at 35.6 million people, and this number is expected to double by 2030 and more than triple by 2050. Moreover, estimated annual costs of dementia reached $604 billion (U.S. dollars) in 2010[3, 4]. With rising prevalence, these costs are expected to increase by 85% by 2030, which would make dementia the most expensive chronic disease associated with aging.

Sleep apnea is a common age-associated type of sleep disordered breathing (SDB), with clinical symptoms including loud snoring, breathing pauses such as choking or gasping during sleep, morning headaches, insomnia, and daytime sleepiness [64-66]. Sleep apnea and risks associated with it, such as obesity, are becoming an increasingly important public health issue for adults [64, 67-71]. The prevalence of sleep apnea varies by age and sex and is more common in older adults and men[65, 72, 73]. It is estimated to be present in 20 to 50% of older adults [65]. For people aged 50-70 years old, 17% of men and 9% of women are estimated to have moderate-to-severe SDB[74].

Sleep apnea is associated with cognitive impairment and dementia in older populations[75, 76]; however, the relationship between pre-existing sleep apnea and incident cognitive impairment and dementia remains poorly characterized. Many existing studies are limited by cross-sectional study designs, small sample size, or short follow-up time [77, 78]. Three cross-sectional studies in populations aged over 65 years found no association between the apnea-hypopnea index and cognitive function [79-81]. By contrast, in a prospective study of 298 women, Yaffe et al. [82] found that SDB was associated with a

71% increased risk of developing mild cognitive impairment (MCI) or dementia over 5 years after adjusting for age, race, body mass index, education level, smoking status, presence of diabetes, and hypertension. A retrospective population-based study also showed increased risk of developing dementia for a Taiwanese population aged over 40 years who attended a national health insurance program [83]. Sleep apnea patients had a 170% increase in dementia risk compared with patients without sleep apnea after adjustment for age, sex, hypertension, diabetes, stroke, and hyperlipidemia during the 5-year follow-up period . Finally, an eight-year study of older adults found only small effects of SDB on decline in attention, but not memory, once other medical comorbidities were included in their statistical models[76].

However, these cohort studies were unable to consider the effect of the genetic risk factor, APOE[84], on risk of dementia. Since APOE is a major unmodifiable risk factor for dementia due to Alzheimer's disease (AD), the most common form of dementia, it is important to understand whether sleep apnea or SDB might differentially influence the risk of dementia based on the status of APOE genotype. To our knowledge, only three studies have explored this association. O'Hara et al. conducted a small cross-sectional study (n=36) and found that SDB was only associated with impairment of verbal memory in APOE ε4 allele carriers [85], while Osorio and colleagues (n=95) found only a trend toward lower CSF Aβ-42 levels in APOE ε4 positive normal older adults with SDB [68]. A second study by Osorio and colleagues based on the Alzheimer's disease Neuroimaging Initiative database (n=2,285) found that SDB was associated with younger age at onset of MCI, and this was not affected by APOE ε4 carrier status [86]. Additional studies are needed to investigate this topic.

Using Prevention of Alzheimer's Disease (AD) by Vitamin E and Selenium (PREADViSE) trial data, which comprises 7,547 male subjects who were free from dementia at baseline, we sought to investigate two research hypotheses (1) older men with self-reported sleep apnea prior to cognitive impairment have an increased risk of dementia, and (2) older men with self-reported sleep apnea have different risks for dementia based on *APOE* allele status.

Methods

Study population and data sources

We conducted a secondary analysis of sleep apnea and incident dementia among 7,547 subjects enrolled in the PREADViSE trial [87]. The PREADViSE trial is an ancillary study to the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (a large prostate cancer prevention randomized controlled trial (RCT) [88] and was designed to evaluate the effectiveness of antioxidant supplements vitamin E and selenium in preventing incident AD and other forms of dementia. PREADViSE investigators were blind to SELECT treatment assignment as of this writing, and so the effects of the antioxidant supplements will not be considered further here. During the recruiting period from 2002 to 2009, PREADViSE enrolled 7,547 non-demented male participants age 62 years and older (age 60 if African American) from 128 participating SELECT clinical sites in the US, Canada, and Puerto Rico. The eligibility criteria for participating in PREADViSE included active SELECT enrollment at a participating site, and absence of dementia and other active neurologic conditions that affect cognition such as major psychiatric disorder, including depression. All 7,547 participants are included in the current study; no further inclusion and/or exclusion criteria were applied for this secondary analysis. The study supplements

in SELECT were discontinued by its Data Safety Monitoring Committee in 2008 following a futility analysis [89], and then PREADViSE and SELECT continued as observational exposure studies. The details of this evolution for PREADViSE can be found in Kryscio et al. [90]. During the RCT phase, SELECT sites used a web-based data collection system to submit data directly to the Cancer Research and Biostatistics Group, who managed the data for SELECT. SELECT provided monthly snapshots of PREADViSE data elements to PREADViSE via a secure file transfer protocol (ftp) site. During the observational phase, data were collected at a single site, the University of Kentucky.

All participants were asked to continue in the exposure study, and 4,271 of 7,547 original PREADViSE volunteers consented to participation (Figure 2.1). PREADViSE was approved by the University of Kentucky Institutional Review Board (IRB) as well as the IRBs at each SELECT study site. Each participant provided written informed consent.

Case Ascertainment

The Memory Impairment Screen (MIS)[91] was used as the primary screening instrument for memory impairment in both the RCT and observational portions of PREADViSE. The MIS was given annually. If participants failed the MIS (that is, the participant scored 5 or less out of 8 on either the immediate or delayed recall portion of the MIS), a second tier screen was administered. An expanded Consortium to Establish a Registry in AD battery (CERAD-e)[92] was used during the RCT period and the modified Telephone Interview for Cognitive Status (TICS-m) [93], was used during the observational study. Both the CERAD-e and the TICS-m assess participants' global cognitive function.

Failure on the secondary screen (T score ≤ 35 on CERAD-e battery or total score ≤ 35 on TICS-m) would lead to a recommendation for a clinic visit with their local physician. Records from the clinic visit were reviewed by 3-5 expert clinicians, including two neurologists and at least one neuropsychologist, for a consensus diagnosis. In cases where the neurologists disagreed in their diagnoses, the study PI made the final determination. Annual screenings were completed in May 2014, and a small number of participants were followed for medical records through August 2015.

The incident dementia cases were identified through two methods. First, as described above, a medical records-based consensus diagnosis was used. Date of diagnosis was assigned as the date of the failed screen. Second, because many participants were reluctant to obtain medical workups for their memory, additional longitudinal measures including the AD8 Dementia Screening Interview [94], self-reported medical history, self-reported diagnosis of dementia, use of memory enhancing prescription drug, and cognitive scores including the MIS, CERAD-e T Score, NYU Paragraph Delayed Recall, and TICS-m were used to identify cases. The diagnostic criteria for the second method were AD8 total of ≥ 1 (at any time during follow-up) to indicate functional impairment [94] plus one of the following: a self-reported diagnosis of dementia, use of a memory enhancing prescription drug (donepezil, rivastigmine, galantamine, or memantine), or cognitive score below cutoffs for intact cognition on any test (for example: 1.5 SDs below expected performance based on age and education normative data[95] . The date of diagnosis was assigned to the earliest event.

Sleep Apnea

All participants were asked during the baseline PREADViSE interview whether they had ever been treated for sleep apnea. Responses were recorded as "yes" or "no."

APOE genotype

APOE genotype was obtained for 7,180 participants (ε2/2: 51 (0.71%); ε2/3: 879 (12.24%); ε2/4: 190 (2.65%); ε3/3: 4,320 (60.17%); ε3/4: 1,599(22.17%); ε4/4: 141(1.96%)). The genotypes were converted to a dummy indicator for at least one ε4 allele, where the presence of at least one ε4 allele was considered a carrier. SAS 9.4® procedure PROC MI was used to impute missing values for the indicator variable (367/7547 (5%)) based on family history of dementia. Four imputed data sets were generated; participants with two or more positive imputations for *APOE* ε4 were coded as *APOE* ε4 positive. *APOE* ε4 positivity is a major risk factor for AD-type dementia [96].

Other Covariates

Other data collected included age at baseline, race, body mass index (BMI), years of education, as well as self-reported indicators of cardiovascular disease (i.e., diabetes, hypertension, and smoking). These are recognized risk factors for dementia [97]. History of significant cognitive or motor impairment due to stroke was a PREADViSE exclusion criterion so baseline prevalence of stroke in the cohort is extremely low (0.6%), thus stroke was not considered further.

Statistical analysis

Chi-square and t-test statistics were used to examine differences in categorical and continuous variables between sleep apnea groups. The log-rank test was used to assess differences in crude cumulative risk of dementia between sleep apnea groups. A series of Cox proportional hazards regression models with self-reported sleep apnea as the

independent variable, survival time to diagnosis of dementia as the dependent variable, and the covariates listed above were applied to simple and multivariable survival analyses, where follow-up time was defined as the period in years between date of PREADViSE study entry and date of dementia diagnosis or, in the absence of dementia, date of last assessment. The multivariable model included main effects for baseline age, years of education, body mass index (BMI), race (black vs. non-black), status of APOE (presence of APOE ε4 or absence of APOE ε4), smoking (yes vs. no), self-reported baseline status of diabetes and hypertension (coded present or absent. Covariates were fixed at baseline. The proportional hazards assumption was tested by checking the interaction between time and each covariate. Interaction terms between history of sleep apnea and each covariate in the model were also tested. None of the interactions were significant. Given the sufficient sample size in each APOE group (n = 2029 and 5518 in APOE ε4 positive group and negative group, respectively), we also evaluated the effect of sleep apnea on risk of dementia stratified by APOE ε4 to evaluate for effect modification between sleep apnea and APOE. All data were analyzed by using SAS 9.4® (SAS Institute, Inc., Cary, NC), and 0.05 was set as the significance level.

Results

Demographic attributes of participants from PREADViSE are shown in Table 2.1. Briefly, 7.3% (552/7547) of the men reported history of sleep apnea at baseline. The absolute difference in baseline age between men with and without sleep apnea was significant but not large (Table 2.1). Men with history of sleep apnea at baseline were significantly more likely to be of black race ($p = 0.02$), smokers ($p<0.001$), have higher BMI ($p < 0.001$), and were more likely to report hypertension ($p<0.001$) and diabetes

($p<0.001$). No significant differences were observed in educational attainment or proportion of *APOE* ε4 carriers.

A total of 310 (4.1%) men were diagnosed with dementia (4.0% for men without sleep apnea, 5.1% for men with history of sleep apnea, respectively; $p = 0.24$). The cumulative incidence accounting for censoring during follow-up was estimated to be 9.3% in the non-sleep apnea group and 24.4% in sleep apnea group (Figure 2.2). However, this difference was not significant due to the relatively small number of dementia cases in the sleep apnea group ($p = 0.14$ by the log-rank test).

Table 2.2 displays hazard ratios for dementia diagnosis from adjusted survival analysis. History of sleep apnea was borderline significant in the adjusted model (HR = 1.44; 95% CI (0.96 – 2.17, $p = 0.08$). In this adjusted analysis, men with sleep apnea were more likely to develop dementia compared to men without sleep apnea. Black race, *APOE* ε4 carrier status, and baseline age were significantly associated with dementia risk. Interaction terms between sleep apnea and each covariate in the model were tested, but none were significant.

Stratified analyses by status of *APOE* ε4 were conducted, and results are shown in Table 2.2. For men without an *APOE* ε4 allele, history of sleep apnea conferred a 66% (95% CI 2%-170%) higher risk of developing dementia (Figure 2.3a). Sleep apnea had no effect when the *APOE* ε4 allele was present (Figure 2.3b).

Discussion

In this study, self-reported baseline history of sleep apnea was borderline significantly associated with risk of dementia after adjustment for confounding ($p = 0.08$). Stratified analysis by *APOE* ε4 carrier status showed that baseline history of sleep

apnea was associated with significantly increased risk of dementia in non-carriers. For the latter, self-reported sleep apnea was estimated to confer a 66% higher risk to develop dementia ($p = 0.0423$), which is consistent with prior studies. Age, race, and *APOE* were significantly associated with the risk of dementia in the multivariable Cox model. We did not find any significant associations for years of education, smoking, BMI, presence of diabetes, or hypertension in either the primary or the stratified analyses with the exception of smoking, which significantly increased risk for *APOE* ε4 carriers. None of the two-way interactions between self-reported sleep apnea and other covariates were significant, including *APOE* ε4, which was likely due to a lack of sufficient statistical power to detect the interaction despite the difference in the stratified analysis.

There are very few prospective studies that have investigated the association between sleep apnea and risk of dementia in an older adult male population. We did not find clear evidence that history of sleep apnea, prior to cognitive impairment, was associated with dementia in men overall, which is similar to the findings reported in Osorio's recent study[86] and several other cross-sectional studies [79-81]. However, our results did show that sleep apnea is significantly associated with dementia risk for men who were *APOE* ε4 allele non-carriers. This is contradictory to the finding of one small cross-sectional study[85], which found that the association existed only for *APOE* ε4 allele carriers, but similar to Osorio et al.'s study [68], in which CSF amyloid beta 42 and tau were not associated with sleep apnea in *APOE* ε4 allele carriers but were associated in noncarriers . Such discrepancies are likely the result of differences in exposure and outcome assessment, residual confounding, covariates adjusted for, sample size, study population, or study design.

Similar to other studies[68, 85], our results indicated an interaction effect of sleep apnea and *APOE* ε4 on the risk developing dementia. This is particularly important considering both the high prevalence of sleep apnea in older populations [65] and the high percentage of APOE ε4 non-carriers in the population (75%) [98]. So far, several prevention trials [76, 99] have been completed with null or inconclusive results. Since the *APOE* ε4 allele is a well-known and non-modifiable risk factor for AD, the findings of this study may help inform prevention strategies for dementia or AD in older men with sleep apnea. Osorio and colleagues [86] suggest that treatment with continuous positive airway pressure (CPAP) may delay onset of MCI. Thus, diagnosis and treatment of sleep apnea in older populations may be helpful in preventing or delaying incident cognitive impairment in the aging population with SDB who are *APOE* ε4 non-carriers.

Possible mechanisms that could explain the association of sleep apnea with risk of incident cognitive decline and dementia include direct effects on cerebral oxygenation and the selective vulnerability of hippocampal neurons to hypoxia, or perhaps augmentation of vascular contributions that have been strongly linked to the development of MCI, AD, and other forms of dementia[82, 100]. Chronic hypoxia has been linked to hippocampal injury that may lower the threshold for the development and or spread of tau-associated neurodegeneration [101]. The development of sleep apnea has also been shown to exacerbate cardiovascular risk factors such as hypertension, and to be strongly associated with obesity, insulin resistance, hyperlipidemia, and the development of the metabolic syndrome[91, 102]. Thus, there may be many ways that sleep apnea contributes to derangements in metabolic pathways that have been strongly associated with increased risk of incident MCI or dementia in the aging population. Indeed, the present data

demonstrate increased prevalence of hypertension and diabetes in those with sleep apnea, although the association with APOE status appeared independent of such conditions in the adjusted analysis, suggesting that other mechanistic factors may be important to consider.

Another possible mechanism for the association of sleep apnea and risk of dementia is that sleep may help regulate brain amyloid-β levels [103, 104]. A recent study in transgenic mice demonstrated that levels of brain amyloid-β increased when both normal and AD mouse models were awake and then decreased during sleep [105]. This diurnal variation in amyloid production could be dramatically altered in persons with sleep apnea or other sleep disturbances[106]. A small study [107] of community-based older adults was able to demonstrate that shorter sleep duration was significantly associated with increased amyloid-β levels. There is also some evidence that APOE might play a role in degradation of amyloid-β [64]. APOE ε4 carriers show lower concentration of amyloid-β in the cerebrospinal fluid, indicating increased amyloid-β deposition in the brain[68]. In the presence of APOE-ε4, any increase in brain amyloid-β associated with sleep apnea may be overwhelmed by that due to APOE ε4 alone. However, it remains unclear why amyloid-β is affected by the sleep cycle or how it depends on the APOE genotype[108].

This study has some limitations. Not all participants who failed the memory screenings were willing to visit their doctors for a memory work-up, so case ascertainment may be less accurate due to lack of medical records. However, application of the secondary dementia criteria (positive AD8 screen, self-reported diagnosis, use of memory enhancing drug, and poor cognitive scores) demonstrated good agreement in the cases where the diagnosis was known (data not shown). Because only a subset of subjects

participated in both the RCT as well as the exposure phases of PREADViSE, some cases may have been missed among the subjects who did not participate in the exposure study. Our data show there were 46.2% participants who had sleep apnea at baseline and did not continue to participate in the study, while 50.1% subjects without sleep apnea in the baseline cohort did not continue. Therefore, the loss of cases would be estimated to be the same for the subjects with and without sleep apnea. We measured sleep apnea with self-report, similar to Osorio et al. [86]. Due to the phrasing of the questionnaire, undiagnosed and or untreated sleep apnea subjects may have been missed [109]. However, because ascertainment of sleep apnea occurred at baseline, it is independent of dementia ascertainment. Therefore, if there is misclassification of sleep apnea exposure, it is non-differential misclassification, and will bias the association toward the null[108], that is, to lessen the degree of association. Thus, our analysis likely underestimates the effect of sleep apnea on dementia risk. Since the study population is all older men, the findings from this study cannot be generalized to older women. However, the current findings align quite well with those reported by Yaffe and colleagues who showed an increased risk for dementia with SDB in older women[82]. Strengths for the study include the large sample and long follow-up. We were also able to consider most well established risk factors for dementia including demographic, genetic, and medical characteristics, including cardiovascular risk factors.

Conclusion

Our study provides evidence that in the absence of APOEε4, sleep apnea may increase the risk of dementia in older men. This may occur through the disruption of brain amyloid-β regulation that occurs during the sleep cycle, or through cerebrovascular

damage, although the exact mechanism remains unclear [110]. Considering the limited number of publications in this area and the inconsistent findings, replication studies with objective measures of sleep apnea, long follow-up, and rigorous methods to diagnose dementia are needed to support this finding conclusively.

From the standpoint of clinical practice, many primary care physicians are unaware of their patients' genetic status and ApoE genotype in particular. However, with adequate screening of SDB symptoms along with other risk factors (e.g., age, ethnicity) our findings along with those of O'Hara et al.[85] and Yaffe et al. [82] we would advise the clinician to work with their patients to address sleep apnea problems as soon as possible given the association with future cognitive dysfunction.

Table 2.1. General Characteristics of the study sample in PREADViSE

Characteristic	All Subjects (N=7,547)	No Sleep Apnea (n=6995)	Sleep Apnea (n=552)	P value
Baseline age[c], y	67.5±5.3	67.6±5.3	66.6±4.5	< 0.001
Education[d], y	15.0±2.7	14.9±2.7	15.1±2.6	NS[b]
Black race	756 (10.0)	685 (9.8)	71 (12.9)	0.02
Baseline smoking[e]	4260 (56.6)	3916 (56.1)	344 (62.4)	0.004
APOE-ε4 (≥1 ε4)	2,029 (26.9)	1876 (26.8)	153 (27.7)	NS[b]
Baseline hypertension	2,998 (39.7)	2703 (38.6)	295 (53.4)	<0.001
Baseline diabetes	858 (11.4)	762 (10.9)	96 (17.4)	<0.001
Baseline BMI[af], kg/m^2	28.5±4.4	28.2±4.2	31.6±5.3	<0.001
Follow-up time, y	5.7±2.8	5.7±2.8	5.5±2.8	NS[b]

[a]BMI: Body Mass Index; [b]NS : Not significant.
[c]*N* = 7546 for age; [d]*N* = 7512 for education; [e]*N* = 7528 for education ; [f]*N* = 7515 for education.

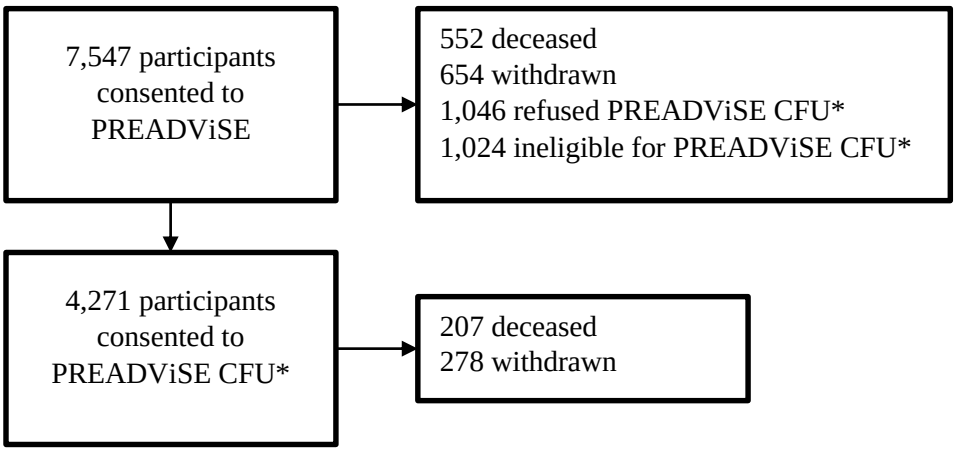
Table 2.2. Association between History of Sleep Apnea and Risk Dementia based on Adjusted Cox Model and Stratified Analysis by APOE ε4 Status

		Stratified Analysis	
	Adjusted HR* & (95% CI)	APOE ε4 carriers (N = 2029)	APOE ε4 non-carriers (N = 5518)
		Adjusted HR[a] & (95% CI)	Adjusted HR[a] & (95% CI)
Sleep apnea	1.44 (0.96-2.17)	1.13 (0.54-2.37)	**1.66 (1.02-2.70)**
Baseline age, 1 year	**1.11 (1.09-1.13)**	**1.14 (1.10-1.17)**	**1.09 (1.07-1.12)**
Education, 1 year	0.98(0.94-1.02)	1.01 (0.94-1.08)	0.95 (0.91-1.01)
Black race	**1.73 (1.19-2.52)**	1.71 (0.97-3.03)	**1.72 (1.05-2.82)**
Baseline smoking	1.20 (0.95-1.51)	**1.55 (1.06-2.26)**	1.03 (0.77-1.38)
APOE ε4 presence	**1.99 (1.58-2.50)**	--	--
Baseline hypertension	0.92 (0.73-1.17)	0.83 (0.56-1.21)	0.98 (0.72-1.33)
Baseline diabetes	1.10 (0.78-1.57)	0.83 (0.43-1.58)	1.29 (0.85-1.97)
BMI	0.99 (0.97-1.02)	1.00 (0.95-1.04)	0.99 (0.96-1.03)

[a]All variables listed in the table were included in the adjusted models.

Note: Results presented are mean±SD or N (%). All PREADViSE participants are male.

Figure 2.1. Participant flow diagram for PREADViSE



*PREADViSE was an ancillary study to SELECT; enrollment was from May 2002 through November 2009 (N=7,547). PREADViSE participants were invited to participate in centralized follow-up (PREADViSE CFU) following the closure of SELECT due to a futility analysis. Some SELECT sites decided not to offer their participants the opportunity to participate in CFU; these participants are listed above as being ineligible. PREADViSE CFU continued to follow participants from August 2010 – August 2015.

Figure 2.2. Probability of dementia by history of sleep apnea (SDB) at baseline. Solid line indicates sleep apnea, dashed line indicates no sleep apnea. Time axis ends at 10 years for consistency among figures.

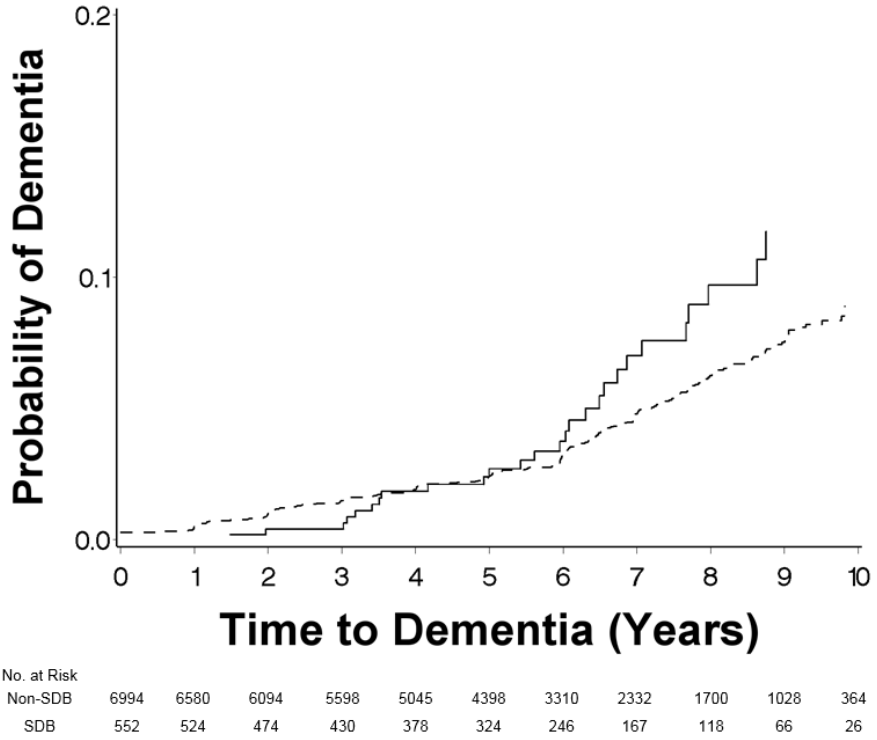
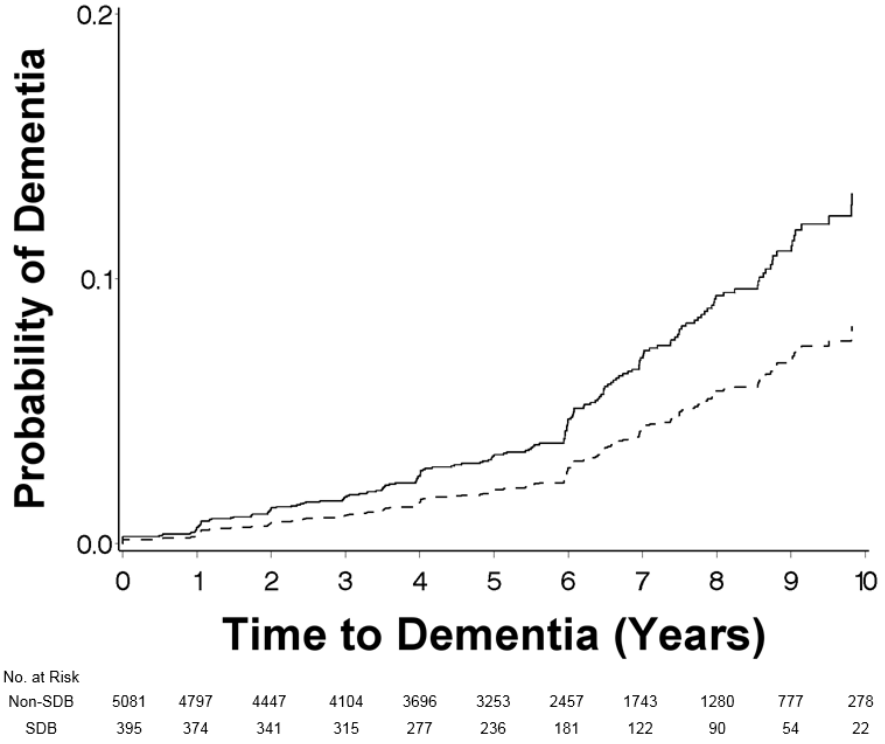
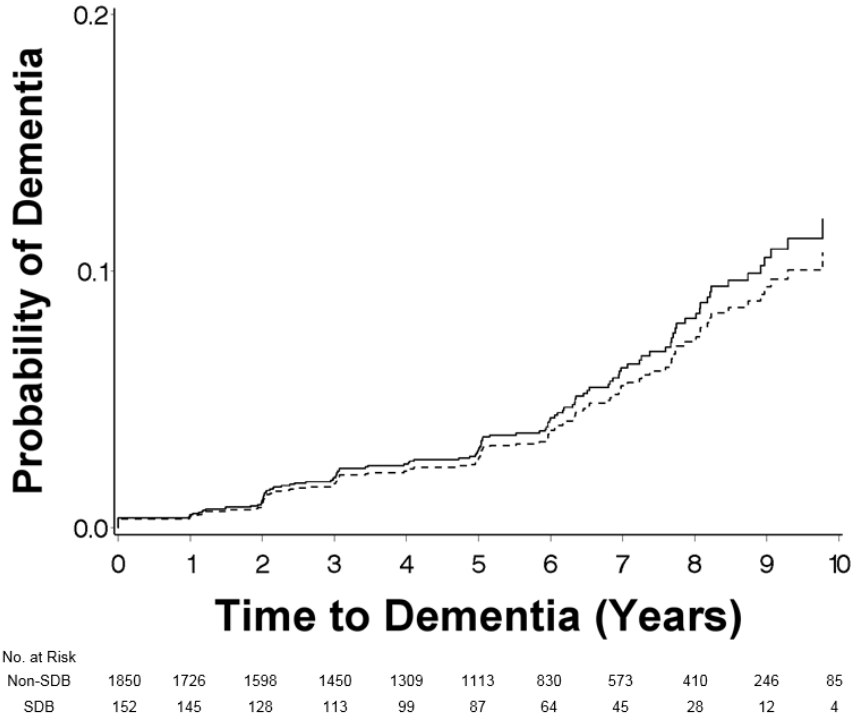


Figure 2.3. Probability of dementia at baseline by history of sleep apnea (SDB) status after adjusting other covariates in *APOE* ε4 non-carriers (a) and carriers (b). These hypothetical participants are white, age 68 at baseline, smoke, have 15 years of education and baseline BMI 28.5 kg/m^2, and comorbidities including presence of hypertension and diabetes. Solid line indicates sleep apnea, dashed line indicates no sleep apnea. Time axis ends at 10 years for consistency among figures.



(a)



No. at Risk											
Non-SDB	1850	1726	1598	1450	1309	1113	830	573	410	246	85
SDB	152	145	128	113	99	87	64	45	28	12	4

(b)

CHAPTER THREE

Evaluating trajectories of episodic memory in normal cognition and mild cognitive impairment: results from ADNI

ABSTRACT

Memory assessment is one of the key components for diagnosis of mild cognitive impairment (MCI) and dementia. Identifying individuals who are likely to follow particular memory trajectories overtime could inform prevention efforts and enhance clinical trial recruitment. To identify the developmental trajectories in memory testing and risk factors associated with these trajectories among cognitively normal and MCI subjects at baseline, 591 Alzheimer's Disease (AD) Neuroimaging Initiative (ADNI) subjects were administered the Rey Auditory Verbal Learning test (RAVLT) for up to 9 years. Group based trajectory modeling was applied separately to identify distinct trajectories in baseline normal and MCI subjects. Six trajectories were identified based on the baseline score of the 30-mintute RAVLT delayed recall score for baseline normal subjects. They can be summarized as three major types: stable (group 3 and 6, ~32%), curvilinear decline (group 4 and 5, ~ 28%), and linear decline (groups 1 and 2: ~ 42% of subjects). In contrast to baseline normal subjects, the 5 trajectories identified for MCI all tended to decline. Age, gender and education were significantly associated with trajectories for both baseline normal and MCI subjects, while *APOE* ε4 allele was only significantly associated with trajectories among baseline MCI subjects. The above results provide evidence for the heterogeneity of developmental memory trajectories. Furthermore, our study also supports prior studies suggesting heterogeneous outcomes for the progression of MCI progressing, even among a highly selected sample of patients.

INTRODUCTION

From a clinical and research perspective, an individual's cognition may be categorized as unimpaired (normal cognition), mildly impaired (mild cognitive impairment or MCI), or moderately to severely impaired (dementia). Over time, normal cognition can stay stable or decline to MCI or dementia. Similarly, MCI can stay stable, progress to dementia, or revert to normal[11]. Therefore, examining potential trajectories within certain populations and identifying individuals who are likely to follow particular cognitive trajectories could inform prevention efforts and enhance clinical trial recruitment by identifying subjects at high risk of cognitive decline.

Memory assessment in neuropsychological testing is one of key elements in the diagnosis of MCI and dementia [111]. One of most commonly used tests for verbal memory assessment is the Rey Auditory Verbal Learning Test (RAVLT**)[112],** which is designed to evaluate episodic memory in persons age 16 and older [113]. The RAVLT provides measures of immediate memory span, learning, and delayed recall, so severity of memory dysfunction and changes over time can be evaluated. For instance, MCI patients show poorer learning than 'recovered' MCI and healthy control groups [114]. The RAVLT is easily administered, so clinicians often prefer it to other list learning tests, especially under conditions of limited assessment time [115]. RAVLT performance is influenced by subjects' demographic characteristics, including age, education, and gender [116, 117].

Poor performance on the test is considered a prognostic marker for MCI and dementia [118-120]. Zhao et al.'s [121] study shows that RAVLT performs better than the Complex Figure Test (CFT) for predicting progression from MCI to AD, and data from the Canadian Study of Health and Aging demonstrate that RAVLT short delayed recall

may be used to predict incident dementia [50]. In the Gothenburg MCI study [122], neuropsychological tests including RAVLT, along with hippocampal volume and cerebrospinal fluid markers, were used to predict progression from MCI to dementia within a follow-up time of two years. They found that a combination of all markers was the most successful to predict dementia, but the RAVLT was the best individual predictor for dementia. RAVLT was also used to distinguish AD from other types of dementia [123, 124].

In this analysis, we explored trajectories of episodic memory using Group Based Trajectory Modeling (GBTM) and longitudinal RAVLT measures for two groups of research participants: Alzheimer's disease Neuroimaging Initiative Phase 1 (ADNI1) subjects with normal cognition at baseline and ADNI1 subjects with MCI at baseline. Key questions focus on what are the trajectories for baseline normal and MCI subjects and whether trajectories differ between baseline normal and MCI subjects over time. In addition, we investigate whether trajectories in cognitively normal subjects and subjects with MCI at baseline predict incident dementia using predicted trajectory membership as a risk factor.

METHODS

Sample population and data sources

Data were obtained and downloaded from the ADNI database (http://adni.loni.usc.edu/) on June 3, 2015. The primary goal of the project is to obtain and assess clinical, imaging, genetic and biospecimen biomarkers related to the development and progression of AD and develop treatments that may slow the progression of AD [125].

Because our interest is focused on longitudinal change, our analysis was limited to ADNI1 participants since they have the longest follow-up. During ADNI1, which began recruiting participants in 2004, 400 MCI subjects, 200 subjects with early AD, and 200 control subjects, all aged 55- 90 years, were targeted for recruitment at 50 study sites across North America (actual enrollment: 397 MCI subjects and 229 normal control subjects, respectively). They were followed-up at 6-month intervals (from study baseline to 9 years). All ADNI research activities were approved by Institutional Review Boards (IRB) at the participating study sites, and all participants provided written informed consent. The University of Kentucky IRB declared this secondary analysis of ADNI data exempt since the ADNI data are de-identified.

Inclusion and exclusion criteria

All analyses for the current study were based on MCI and control subjects who enrolled into ADNI1 (actual enrollment: 397 MCI subjects and 229 normal control subjects, respectively) and had any follow-up visits in ADNI 1, ADNIGO, or ADNI2. Fourteen subjects (1 American Indian, 12 Asian, and 1 more than one race) were excluded from the analysis due to small number in their race categories. Twenty-one subjects with only one visit were also removed from the analyses, which left 591 total subjects for analysis: 219 normal subjects and 372 MCI subjects.

Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT is a list-learning task that measures auditory verbal memory [126]. The RAVLT is conducted using two 15-item lists of unrelated words (List A and List B) that are read to the participant in a series of trials. To begin, List A is read to the participant, and the participant is asked to repeat as many of the 15 words as they can,

and the number of correct words is recorded. This procedure is repeated in another 4 trials, which results in 5 learning trial scores. Then the examiner reads the second list of 15 words (List B) to the participant, and the participant is asked to recall as many of words in List B as possible. Next, the participant is again asked to recall the words in List A, and the number of words (immediate recall score) correctly recalled is recorded. The participant is then given different tasks to do for 30 minutes. After 30 minutes, the participant is asked again to recall as many words as they can from List A, and the number of correct words (30-minute delayed recall) is recorded. Last, the participant is asked to recognize the words in List A when presented a sheet containing the 15 List A words plus 15 distractor words, and examiner records the number of successes (recognition score).

In the current study, the 30-mintute delayed recall score, which ranges from 0 to 15 [127], is the outcome of interest.

APOE genotype

APOE genotype which is significantly associated with cognitive trajectory [128] was obtained for all 591 participants (ε2/2: 2 (0.34%); ε2/3: 46 (7.78%); ε2/4: 13 (2.20%); ε3/3: 281 (47.55%); ε3/4: 199 (33.67%); ε4/4: 50(8.46%)). The genotypes were converted to an indicator for a carrier of at least one ε4 allele.

Covariates

Covariates of interest included age at baseline, race, gender, smoking information, body mass index (BMI) at baseline, years of education, as well as self-reported indicators of cardiovascular disease risk (i.e., diabetes, and hypertension) and sleep apnea. Age at baseline was calculated based on the participant's birthdate and exam

date. Race was coded as a dummy variable: 0 (as black) and 1 (as White). Similarly, smoking was coded as 0(non-smoker) and 1(current smoker). Since ADNI collects medical history as single-field text strings (variable "mhdesc"), the self-reported status of hypertension, diabetes, and sleep apnea was extracted by searching for keywords. For example, the subjects with sleep apnea were identified by first converting all "mhdesc" text string values to uppercase, and then a search for the text string 'SLEEP' was used to find subjects who reported sleep problems. Then each identified case was checked individually to confirm sleep apnea. A similar procedure was conducted for status of hypertension (keywords: "HYPERTENSION", "HIGH BLOOD PRESSURE") and diabetes (keyword: DIABETES). Misspelled conditions in the raw data were identified when each individual value was checked. These three variables were coded as dummy variables (0 = not reported and 1= reported).

Statistical Analysis

Baseline differences between normal and MCI subjects were assessed with Chi-square and t test statistics except that number of examinations and months of follow-up were conducted through Mann-Whitney Wilcoxon test. GBTM [129, 130] was applied to identify different longitudinal trajectories and estimate mean level of RAVLT 30-minute delayed recall scores for normal and MCI subjects separately. Trajectory analysis assumes that the study population is a mixture of several latent subgroups. According to this hypothesis, in each latent subgroup the 30-minute delayed recall score follows a distinct trajectory over time. To implement GBTM, the outcome was modeled first as a function of time and latent groups were identified. Next, the proportion of the population that follows each latent trajectory was estimated. Individuals were assigned to specific

latent groups based on the largest posterior probability of group membership for each individual. Finally, the analyses examined how the probability of trajectory group membership varied with covariates versus an arbitrary reference trajectory group. In the present study, covariates of interest included age, race, gender, *APOE* ε4 carrier status, education, hypertension, diabetes, sleep apnea, BMI, and smoking status.

To find the best fitting model to predict trajectory group membership, various models including all 10 covariates were fitted for 2 to 6 trajectories (inclusive) [44] and all combinations of orders (quadratic was the highest order) of each group. Bayesian Information Criterion (BIC) was applied to select the best number of groups and orders [43]. Then log-likelihood ratio tests were applied to reduce the number of covariates in the model. Censored normal distribution (CNORM) was applied to normal subjects, while Zero Inflated Poisson (ZIP) for modeling excess zero counts were used for MCI subjects based on histograms of the outcome in each study population (data not shown). To fit CNORM in the normal sample, the 30-minute delayed recall score was standardized by subtracting the baseline sample mean (7.5) and dividing by the sample standard deviation (3). The ZIP model assumes that some zeros occur in the Poisson process, and others are from a separate always zero generating process. There are two processes in the ZIP model – one is to determine if the individual is eligible for a non-zero response, the other estimates the mean of a Poisson distribution from which a count of response can be generated for eligible individuals. Furthermore, the eligibility of a non-zero response for an individual may vary with time. These two processes are fit simultaneously with two separate regression models: logistic regression to model the probability of being eligible for a nonzero count, and Poisson regression to model the size of the count. For simplicity,

we assumed that the probability logit for being eligible for a zero count in the ZIP model was common to all trajectory groups and constant over time.

The final fitted model provides descriptive information on the estimated groups, including (1) posterior probabilities of an individual belonging to one of the identified groups, (2) the proportion of each study group following the same latent trajectory, (3) regression parameters to define the shape of the trajectories over time (intercept only, linear, and quadratic in the present study), (4) risk and protective factors associated with membership in a trajectory group.

All data were analyzed by using PC-SAS 9.4® (SAS Institute, Inc., Cary, NC), and 0.05 was set as the significance level. Group trajectory analyses were carried out using the SAS procedure PROC TRAJ [129, 130].

Results

Table 3.1 presents the characteristics of participants overall and participants by cognitive status at baseline. Normal subjects were followed up longer than MCI subjects ($p < 0.001$). Also, normal subjects were older ($p = 0.039$), more highly educated ($p = 0.049$), more likely to be female ($p = 0.007$), and had higher BMI than MCI subjects ($p = 0.037$). Normal subjects comprised fewer *APOE-ε4* allele carriers and subjects with sleep apnea than MCI subjects. Over 91% of subjects had > 3 examinations. There were 2476 total observations from MCI subjects and 1541 observations from normal subjects.

Potential groups identified by GBTM

GBTM identified distinct latent groups in the normal and MCI study samples. For normal subjects, 6 latent groups were identified (Figure 3.1) while for MCI subjects 5 groups were identified (Figure 3.2) based on the best BIC values among the candidate trajectory models. Table 3.2 shows descriptions of the trajectories for normal MCI subjects, including the shape of each group trajectory and the number of probable members. Trajectories were numbered in order of the estimated mean of 30-minute delayed recall at baseline.

Baseline normal subjects showed three types of trajectories over time: stable (groups 3 and 6: ~30% of subjects), curvilinear decline (groups 4 and 5: ~28% of subjects), and linear decline (groups 1 and 2: ~ 42% of subjects). Table 3.3 shows characteristics for the trajectory groups. For normal subjects, Group 6 is youngest, and has the most male subjects and most years of education. Subjects in group 3 are oldest, group 5 has the most year of education and most male subjects in MCI group. As shown in Figure 3.1, group 6 (n = 22) and group 3 (n = 44) remained relatively stable over 9 years of follow-up but had different intercepts. Group 5 (n = 30) showed slow curvilinear decline during the first 4 years of follow-up and faster decline after 4 years, and Group 4 (n = 31) revealed mild curvilinear decline. Table 3.3 shows the observed frequency of cognitive status at end of follow-up by assigned group memberships. The majority of subjects assigned to Groups 3 and 6 remained cognitively normal at the end of follow-up, and only 5 subjects in Group 3 progressed to MCI status. No subjects in Groups 3 or 6 progressed to dementia by the end of follow-up. Groups with members most likely to develop dementia by end of follow-up were Groups 1 (18%) and 5 (17%). Details of parameter estimates for each trajectory are included in Table 3.2.

In contrast to groups identified for normal subjects, all potential trajectory groups for MCI subjects showed the tendency to decline, with the exception of group 2, which starts near and stays around "0" (floor effect). Subjects in Group 1(n = 143) and Group 2 (n = 66) were most likely to develop dementia by end of follow-up, with over 70% of each group progressing (Table 3.3). Subjects in Group 3 (n = 66) had a slightly better chance to remain in MCI (52%) than progressing to dementia (48%), while the majority of subjects in Groups 4 (70%) and 5 (65%) remained MCI. Interestingly, 11% subjects in group 4 (n = 73), and 22% subjects in Group 5 (n = 23) had reverted to normal cognition by the end of follow-up. None of the MCI subjects in Groups 1 – 3 reverted back to normal status by the end of follow-up.

For all 6 normal groups and all 5 MCI groups (Table 3.2), the averages of the posterior membership probabilities were greater than 0.7, which indicates that the models are acceptable based on the Nagin's 'rule of thumb' on minimum average posterior probability [131].

Risk factors associated with probability of trajectory group membership

Table 3.4 presents the parameter estimates for the risk factors associated with trajectory group membership. The comparison group is Group 4 for both normal and MCI subjects, which was arbitrarily selected. Based on BIC and log-likelihood ratio test, age, BMI, and education were retained in both the 6-group model for normal subjects and 5-group MCI model (Table 3.4) , while gender only stayed in model for normal subjects, and *APOE* ε4 was only in the model for MCI subjects (Table 3.4). Demographic variables associated with group memberships among baseline normal subjects (vs. Group

4) included female gender (p = 0.02 for Group 6), older age (p = 0.03 for Group 2) and higher education (p = 0.02 for Group 2, and p = 0.01 for Group 3). For example, in group 2 for baseline normal subjects, it was estimated that each additional year of education increase reduces probability of belonging to Group 2 vs. the probability of belonging to Group 4 by 22% (probability ratio[PR] = 0.78) ,which means that subjects with higher education were more likely to be classified into Group 4 than Group 2. Similar effects were observed for Group 1 vs. Group 4.

For baseline MCI subjects, *APOE* ε4 allele was a risk factor for being in Groups 1 and 2 (p = 0.002 and p < 0.001, respectively) which means that *APOE* ε4 allele carriers would be more likely to be Group 1 or Group 2 than Group 4 (see Table 3.3). The *APOE* ε4 allele carriers increased the PR of belonging to Group 1 vs. belonging to Group 4 by 85%, and the probability of belonging to group 2 vs. belonging to group 4 by 388%, holding other covariates constant in the model. Based on Table 3.4, age is not significant but kept in the model, which may suggest that age cannot distinguish the rest groups from reference Group 4, but it may distinguish Group 3 from Group 2 (data not shown). BMI was significant in Group 1 (p = 0.02) and 2(p <0.001) which suggests higher BMI will move subjects out of Group 1 or Group 2 into Group 4.

Discussion

In the current study, we estimated the trajectories of RAVLT 30-minute delayed recall scores over 9 years of follow-up in baseline ADNI normal and MCI subjects. Normal subjects showed three patterns: stable, linear decline, and curvilinear decline, while trajectories for MCI subjects were more heterogeneous. For normal subjects,

subjects assigned to stable trajectory groups (Groups 3 and 6) were more likely remain cognitively intact. Notably, none of the subjects in Groups 3 or 6 converted to dementia during the 9-year study period. Normal subjects in Group 1 (which had the lowest estimated baseline mean score) and Group 5 (which showed faster decline after 4 years follow-up) were more likely to develop dementia compared to other groups of normal subjects. Different from baseline normal subjects, MCI subjects in Groups 1 and 2 (which account for ~56% of all baseline MCI cases) were more likely to progress to dementia, while Group 3 subjects had a close chance to stay at the MCI stage (52%) or progress to dementia (48%). Subjects in Groups 4 and 5 were more likely to stay in the MCI stage, but they also show the most potential to revert back to clinically cognitive normal which provided evidence for supporting disparate outcomes for MCI subjects.

A finding of this study was that baseline normal subjects had two trajectory groups that, on average, exhibited stable memory; none of them progressed to dementia by end of follow-up. Also, our study found that a small percentage of baseline normal subjects demonstrated stable or improving memory trajectories in mean level, and then suffer fast decline; these subjects had higher probability to progress to MCI/dementia.

In comparison with three trajectory groups in AIBL study (Australian Imaging, Biomarkers and Lifestyle) [132] and four groups in WHICAP (Washington Heights Inwood Columbia Aging Project)[128], we identified 6 trajectory groups for baseline normal subjects. Similar to the above two studies, we identified stable and decline groups for baseline normal subjects and two curvilinear groups as well. Group 5 was stable for the beginning 4 years, then showed fast decline in the following year which suggested that those subjects were initially cognitively stable or even better but

experience an event associated with cognitive impairment and dementia, such as restricted mobility [133-135]. Comparing to 65.5% and 50% subjects assigned into stable groups for AIBL study and WHICAP, respectively, we had proportionally less subjects assigned to the stable groups (Group3 and Group 6; about 30%). This inconsistency may be due to the larger number of groups identified in our study, the longer follow-up time in our analyses (9 years vs. 4.5 years in AIBL study and 6 years in WHICAP), as well as different inclusion and exclusion criteria within each study.

To our knowledge, this is one of a few studies to explored memory trajectories in MCI subjects. Although most of the potential trajectory groups show a tendency to decline except Group 2 stay around 0 over time, 11% and 22% MCI subjects in Groups 4 and 5, respectively, reverted back to normal cognitive status (determined by clinical diagnosis), and 19% and 13% progressed to dementia, respectively, which supports the evidence for disparate outcomes often reported in MCI subjects [43, 136, 137]. The trajectories in Groups 1 and 2 began with lower scores (Table 3.1s in the appendix shows mean of RAVLT 30-minute delayed recall around 0), and the majority (73% in Group 1 and 71% in Group 2) progressed to dementia, which may indicate the subjects in these two groups were already at a late stage of MCI at enrollment. Based on our results, the rate of incident dementia from MCI may be correlated with the baseline mean of RAVLT 30-minute delayed recall. The higher the baseline mean value was, the lower the conversion rate. Overall, the 9-year cumulative incidence of dementia from MCI was 53% (roughly 6% per year), which is comparable to the 5-year cumulative incidence of dementia from MCI reported in specialist centers (39%, or roughly 8% per year)[138].

Different demographic variables were associated with trajectory membership for normal and MCI subjects. For baseline normal subjects, older age and less education were significantly associated with being in the "linear decline" group (Group 2), and subjects with less education is more likely to be in Group 3 than being Group 4. Being female was associated with a stable trajectory (Group 6), which was confirmed in Table 3.3 (female 77%), but was inconsistent with Lin's study [139]. In baseline MCI subjects, genetic risk factor *APOE*-ε4 allele and/or lower BMI was associated with lower memory scores (Group 1 and Group 2).

Strengths and limitations

The strengths of this study included relatively large baseline sample size (219 for normal and 372 for MCI), frequent clinical assessments, standardized diagnostic criteria for cognitive status, and standardized data collection procedure across multiple study sites. This allowed more comprehensive investigation of memory trajectories and their relationship with risk or protective factors using long follow-up and multiple visits (up to 12 visits for over 9 years).

One potential limitation for the study sample is that the subjects in ADNI may not be representative of the general population of older adults in the United States. We focused only on participants from ADNI1 in order to obtain participants with longer follow-up, so we excluded the early MCI subjects recruited in ADNIGO and late MCI subjects enrolled in ADNI2 due insufficient follow-up. The diagnosis of MCI was made without further specifying the subtype of MCI (i.e., amnestic, nonamnestic, single domain, multiple domain), thus a more homogeneous set of trajectories may exist within subtypes of MCI subjects. In the future studies, we aim to validate these trajectories using

MRI or biomarker data, and identify unique trajectories for subsets of MCI subjects (i.e., early mild cognitive impairment (EMCI), early mild cognitive impairment (LMCI)).

Another limitation is the uncertainty of group membership. Even though the average posterior probability is high, the parameter estimates in the model are biased. Also in general, although demographics and baseline scores may provide some guidance, patients cannot be assigned with accuracy to any trajectory at initial visit but only after the subject has been followed for several assessments.

CONCLUSION

Group based trajectory modeling can be used to identify distinct latent subgroups of older subjects based on memory trajectory. The relationship between trajectory group and cognitive status at the end of study period confirmed that memory trajectory is an excellent indicator of dementia. If trajectory group membership can be identified reliably during early follow-up, such work will allow clinicians to monitor or predict progression of individual patient's cognition.

Table 3.1. Subject characteristics for ADNI1 participants and by cognitive status

Characteristic	All Subjects (N=591)	Normal (n=219)	MCI (n=372)	P value[d]
Number of examinations(range 2 – 12)				
1/2/3/4+	0/27/25/539	0/7/4/208	0/20/21/331	
Mean ±SD	7±3	8±3	7±3	
Median	7	9	6	<0.001
Months of follow-up (range 6 – 108)				
Mean ±SD	54±31	64±30	49±29	
Median	48	72	36	<0.001
Baseline age[b], y	75.2±6.6	75.9±5.1	74.8±7.3	0.039
Education[b], y	15.8±2.9	16.1±2.8	15.6±3.0	0.049
White race[c]	562 (95.1)	204 (93.2)	358 (96.2)	0.094
Male gender[c]	352 (59.6)	115 (52.5)	237 (63.7)	0.007
Baseline smoking[c]	235 (39.8)	84 (38.4)	151 (40.6)	0.592
APOE-ε4 (≥1 ε4 allele) [c]	262 (44.3)	58 (26.5)	204 (54.8)	<0.001
Baseline sleep apnea[c]	60 (10.2)	14 (6.4)	46 (12.4)	0.020
Baseline hypertension[c]	278 (47.1)	105 (48.0)	173 (46.6)	0.757
Baseline diabetes[c]	49 (8.3)	19 (8.7)	30 (8.1)	0.802
Baseline BMI[ab], kg/m^2	26.4±4.1	26.8±4.3	26.1±4.0	0.037

[a]BMI: Body Mass Index ; [b] mean ± standard deviation; [c]count (%). [d] P values for continuous variables from t test statistics and P values for categorical variables from Chi-square test except that p values for number of examinations and months of follow-up were from Mann-Whitney-Wilcoxon.

Table 3.2. Description of identified groups from the trajectory modeling

Identified group membership	%[a]	n[b]	Trajectory polynomial[c]	P value for trajectory polynomial[d]	Parameter estimates of trajectory group[e]			Posterior probability[f]
					Intercept(SE)	Slope(SE)	Quadratic(SE)	Mean± SD(min)
Baseline normal								
1	15.1	33	Linear	<0.001	-1.48(0.05)	-0.11(0.01)	-	94.9±11.6(62)
2	26.6	58	Linear	<0.001	-0.56(0.04)	-0.11(0.01)	-	95.9±9.7(51)
3	20.2	44	Quadratic	0.51	-0.0001(0.01)	0.001(0.03)	0.003(0.004)	92.6±13.2(56)
4	14.2	31	Quadratic	<0.001	0.67(0.07)	0.27(0.04)	-0.03(0.006)	91.7±14.7(54)
5	13.8	30	Quadratic	<0.001	0.47(0.07)	0.11(0.06)	-0.05(0.006)	92.8±12.3(52)
6	10.1	22	Linear	<0.001	1.74(0.06)	0.11(0.02)		97.0±10.3(54)
Baseline MCI								
1	38.5	143	Linear	<0.001	0.25(0.16)	-0.70(0.08)	-	95.5±9.3(53)
2	17.8	66	Quadratic	0.012	-9.94(2.63)	4.20(1.47)	-0.53(0.21)	83.5±9.5(61)
3	17.8	66	Linear	<0.001	1.18(0.08)	-0.14(0.03)	-	87.3±15.2(38)
4	19.7	73	Linear	0.0159	1.73(0.05)	-0.02(0.01)	-	90.5±13.5(51)
5	6.2	23	Linear	0.6103	2.34(0.04)	-0.01(0.01)	-	95.8±10.6(52)

Note: %[a] = percent of subjects were assigned in the trajectory group based on the greatest posterior probability for the subject; b= number of subjects in the trajectory group; c = highest term of polynomial for the trajectory group; d = p value for highest term of polynomial for the trajectory group; e = parameter estimates in each trajectory group(intercept, slope, quadratic), SE = standard error of each parameter estimate; f = average and standard deviation of greatest posterior probability for all subjects assigned in the trajectory group, min = minimum posterior probability in the trajectory group.

Table 3.3. Characteristics of the subjects in each trajectory group

Potential Trajectory group	n	Age[a]	Education[a]	Female[b]	APOE-ε4[b]	BMI[a]	Follow-up time[a] (Months)	Baseline RAVLT[a]	Cognitive Status at end of follow-up[c]		
									Normal	MCI	Dementia
Baseline normal Subject											
1	33	76.4±5.4	16.2±2.6	42.4	30.3	25.1±3.6	52.4±30.4	3.3±1.8	19(57.6)	8(24.2)	6(18.2)
2	58	77.1±5.2	15.6±2.9	34.5	25.9	27.4±4.0	56.9±31.4	6.2±2.7	39(67.2)	14(24.1)	5(8.6)
3	44	76.0±4.9	15.3±2.9	56.8	22.7	26.7±4.1	69.3±28.7	6.9±3.0	39(88.6)	5(1.4)	0(0.0)
4	31	75.0±5.7	16.9±2.8	41.9	19.4	27.5±3.8	70.8±28.1	9.4±3.1	28(90.3)	2(6.5)	1(3.2)
5	30	75.6±4.8	16.1±3.3	50.0	33.3	26.1±5.6	73.2±27.9	9.1±2.2	20(66.7)	5(16.7)	5(16.7)
6	22	74.4±3.5	17.2±1.8	77.3	31.8	28.0±5.0	68.2±29.3	12.9±2.3	22(100.0)	0(0.0)	0(0.0)
Baseline MCI subject											
1	143	73.9±7.3	15.3±3.2	42.0	61.5	25.5±3.7	44.2±25.9	1.5±1.6	0(0.0)	39(27.3)	104(72.7)
2	66	75.1±7.1	15.9±2.5	34.9	78.8	25.2±3.5	38.9±27.4	0±0	0(0.0)	19(28.8)	47(71.2)
3	66	77.5±5.9	14.8±3.1	19.7	42.4	27.4±4.1	55.4±29.1	3.3±1.9	0(0.0)	34(51.5)	32(48.5)
4	73	73.9±8.3	16.0±2.7	34.3	37.0	26.9±4.3	54.3±33.0	5.6±3.0	8(11.0)	51(69.9)	14(19.2)
5	23	74.0±7.5	17.2±2.3	56.5	34.8	26.2±4.6	68.6±30.1	10.1±3.2	5(21.7)	15(65.2)	3(13.0)

Note: RAVLT = Rey Auditory Verbal Learning Testing; a =mean ± standard deviation; b=percentage; c= count (%).

Table 3.4. parameter estimate for risk factors associated with each trajectory group

	Trajectory group	Parameter	Estimate (SE)[a]	p-value
Normal Subjects				
	1	Intercept	0.93 (2.95)	0.75
		Age	0.06 (0.04)	0.16
		BMI	-0.12 (0.06)	0.06
		Gender	-0.41 (0.60)	0.49
		Education	-0.10 (0.11)	0.40
	2	Intercept	-1.31 (3.60)	0.72
		Age	0.09 (0.04)	0.03
		BMI	0.01 (0.05)	0.90
		Gender	-0.98 (0.55)	0.08
		Education	-0.24 (0.11)	0.02
	3	Intercept	8.10 (2.52)	0.001
		Age	-0.02 (0.04)	0.67
		BMI	-0.05 (0.06)	0.36
		Gender	-0.26 (0.59)	0.65
		Education	-0.29 (0.11)	0.01
	5	Intercept	0.19 (3.34)	0.96
		Age	0.04 (0.05)	0.42
		BMI	-0.05 (0.06)	0.42
		Gender	-0.07 (0.62)	0.91
		Education	-0.10 (0.13)	0.44
	6	Intercept	-2.88 (5.00)	0.57
		Age	-0.06 (0.06)	0.33
		BMI	0.02 (0.06)	0.69
		Gender	1.74 (0.73)	0.02
		Education	0.22 (0.15)	0.14
MCI subjects				
	1	Intercept	2.70 (1.90)	0.16
		Apoe4	1.05 (0.33)	0.002
		Age	0.02 (0.02)	0.44
		BMI	-0.09 (0.04)	0.02
		Education	-0.08 (0.05)	0.14
	2	Intercept	7.76 (1.91)	0.00
		Apoe4	1.77 (0.47)	<0.001
		Age	-0.03 (0.02)	0.26
		BMI	-0.21 (0.05)	<0.001
		Education	-0.11 (0.07)	0.09
	3	Intercept	-1.96 (2.97)	0.51
		Apoe4	0.40 (0.43)	0.35
		Age	0.06 (0.03)	0.07
		BMI	-0.01 (0.05)	0.83
		Education	-0.14 (0.07)	0.04
	5	Intercept	-1.63 (3.52)	0.64
		Apoe4	-0.15 (0.56)	0.79
		Age	-0.01 (0.03)	0.75
		BMI	-0.03 (0.07)	0.64
		Education	0.13 (0.11)	0.22

Note: all results of parameter estimates were derived by using group 4 as reference group in both normal and MCI subjects; [a] SE = standard error

Figure 3.1. Model based trajectories identified for baseline normal ADNI participants

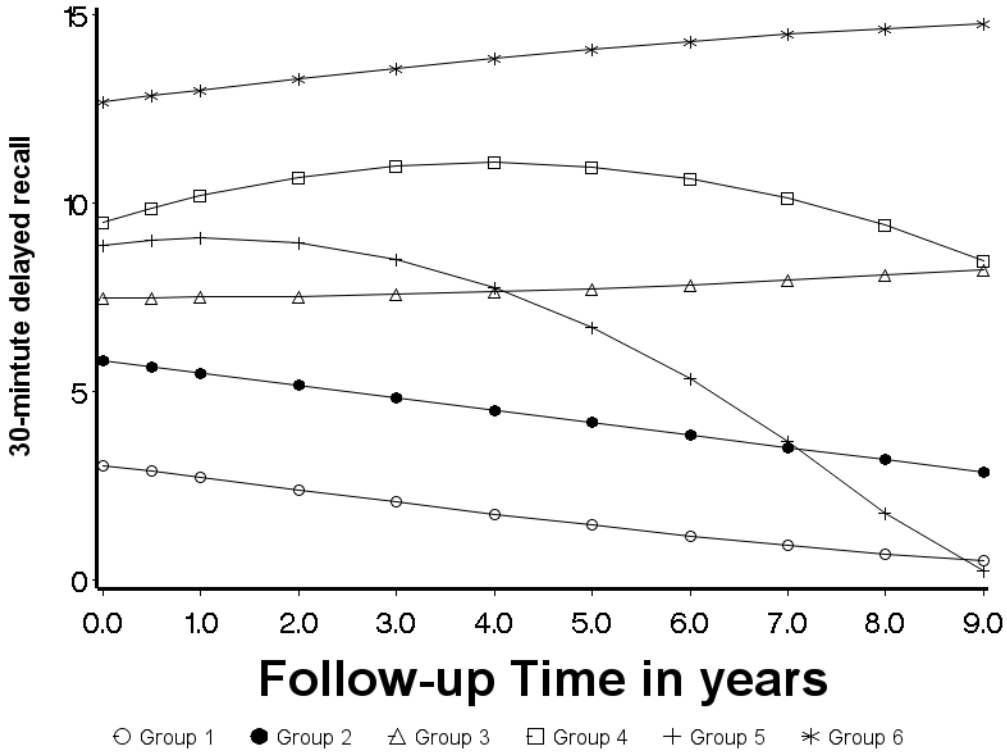
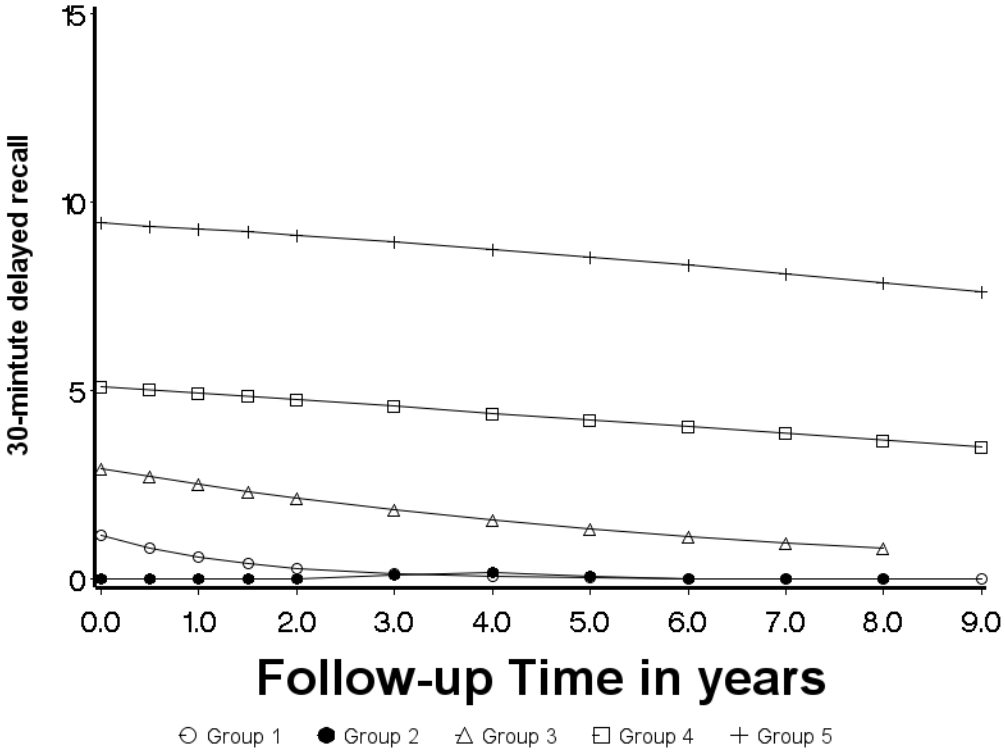


Figure 3.2. Model based trajectories identified for baseline MCI ADNI participants



CHAPTER FOUR

Comparison between neural network and logistic regression for dementia prediction: Results from the PREADViSE trial

ABSTRACT

Two reviews summarized nearly all studies about parametric predictive models and suggested that none are recommended for use in population dementia diagnostic screening. Therefore, further investigation needs to be conducted on this topic. The goal of this study was to apply logistic regression (parametric method) and neural network (non-parametric method) in a large Alzheimer's disease prevention trial to compare the predictive performance of two methods. Significant covariates were entered into multivariate logistic regression for prediction modeling. Backward elimination was applied to select the final logistic regression model. Neural network was performed through the R package "Neuralnet" by using the same covariates as in the final logistic regression model. Results show that neural network had a slightly better predictive performance (area under curve (AUC): 0.732 in neural network vs. 0.725 in logistic regression). Overall, neural network has better in sensitivity (83.2%) and negative predicative value (98.0%) than in logistic regression's sensitivity (72.6%) and negative predictive value was (42.7%), but not in the positive predictive value (10.0% vs. 42.8%). Furthermore, in logistic regression, higher education was associated with deceased probability of dementia. Older age, the presence of the *APOE* ε4 allele and the presence of a reported memory change were positively associated with having dementia. Similar effects were illustrated for covariate presence of *APOE* ε4 allele and memory change in

neural network, but not for education. Based on the result in neural network, the effect of education depends on age, presence of *APOE* ε4 allele and memory change. In conclusion, neural network performed slightly better than logistic regression in sensitivity and negative predictive value, and it also is able to reveal complicated relationships among covariates.

INTRODUCTION

The rising of prevalence dementia has become a major concern for public health as disability associated with dementia, especially at the late stage, leads to high costs personally, socially and economically. Early identification of individuals with high risk of dementia may be of great importance to prevent or intervene dementia onset. To identify these high-risk individuals as earlier as possible, developing an effective predictive or prognostic models with risk factor is regarded as research priority. So far, numerous studies have been conducted to find a useful prediction model.

Many parametric prediction models have been predominantly developed from logistic regression [47-50] or proportional hazards regression analysis [51-56]. For non-parametric models, the classification tree is the most often used method [60, 61]. Alternative approaches, also include non-parametric statistical learning methods such as random forest [62] and neural network analyses[63]. Covariates used in the majority of predictive modeling studies include demographic variables, such as age, education, body mass index (BMI), medical comorbidity (e.g., history of cardiovascular disease) or neuropsychological or cognitive tests. Recently, studies have incorporated genetic risk factors and imaging data into predictive models [53, 140]. However, studies have also argued that non-genetic risk factors and neuroimaging variables have not significantly increased

discriminative accuracy [140], and that these data are often difficult and expensive to obtain [141]. Furthermore, evidence suggests that a third of Alzheimer's disease (AD) cases worldwide may be due to modifiable risk factors [142].

Two systematic reviews, which summarized nearly all parametric research methods for prediction of dementia risk in the past decades [45, 46] , concluded that despite the significant increase in the number of risk modeling studies, the predictive accuracy of these parametric models has not changed to a significant degree (range 0.49-0.91 in 2010 review, and 0.49-0.89 in the 2015 review) , and none of the methods are recommended for dementia risk prediction in the population setting due insufficient consideration of sample selection, model diagnostics, and model validation [45, 46].

In this study, we aim to compare the predictive performance between neural network and logistic regression using mainly mental status and self-reported data from the Prevention of Alzheimer 's disease with Vitamin E and Selenium (PREADViSE) trial and also including a known AD genetic risk (APOE genotype) and clinical diagnosis of dementia) to construct a predictive model.

METHODS

Study sample and data sources

The PREADViSE trial was an ancillary study to the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (a large prostate cancer prevention randomized controlled trial (RCT))[88] and was designed to evaluate the effectiveness of antioxidant supplements vitamin E and selenium in preventing incident AD and other forms of dementia. During the recruiting period from 2002 to 2009, PREADViSE enrolled 7,547 non-demented male participants age 62 years and older (age 60 if African American)

from 128 participating SELECT clinical sites in the US, Canada, and Puerto Rico. The eligibility criteria for participating in PREADViSE included active SELECT enrollment at a participating site, and absence of dementia and other active neurologic conditions that affect cognition such as major psychiatric disorder, including depression.

The SELECT study supplements were discontinued by its Data Safety Monitoring Committee in 2008 following a futility analysis on its primary endpoint of prostate cancer incidence [89], and then participants in PREADViSE and SELECT were invited to continue as participants in observational cohort studies. All participants were invited to continue in the cohort study, and 4,271 of 7,547 original PREADViSE volunteers consented to participation. In order to maximize the consistency and completeness of follow-up, only participants who were screened in both the RCT and exposure phases of PREADViSE are included in the current study (N=3784). PREADViSE was approved by the University of Kentucky Institutional Review Board (IRB) as well as the IRBs at each SELECT study site. Each participant provided written informed consent.

Mental status screening

The Memory Impairment Screen (MIS) [91] was used as the primary screening instrument for memory impairment in both the RCT and observational portions of PREADViSE. The MIS was given annually. If participants failed the MIS (that is, the participant scored 5 or less out of 8 on either the immediate or delayed recall portion of the MIS), a second tier screen was administered. An expanded Consortium to Establish a Registry in AD battery (CERAD-e) [92] was used during the RCT period and the modified Telephone Interview for Cognitive Status (TICS-m)[93] , was used during the observational

study. Both the CERAD-e and the TICS-m assess participants' global cognitive function. Failure on the secondary screen (T score ≤ 35 on CERAD-e battery or total score ≤ 35 on TICS-m) would lead to a recommendation for a clinic visit with their local physician. Records from the clinic visit were reviewed by 3-5 expert clinicians, including two neurologists and at least one neuropsychologist, for a consensus diagnosis. In cases where the neurologists disagreed in their diagnoses, the study PI made the final determination. Annual screenings were completed in May 2014, and a small number of participants were followed for medical records through August 2015.

Covariates

APOE genotype was obtained for 3681 participants (ε2/2: 26 (0.71%); ε2/3: 459 (12.47%); ε2/4: 86 (2.34%); ε3/3: 2240 (60.85%); ε3/4: 808(21.95%); ε4/4: 62(1.68%)). These genotypes were converted to a dummy indicator for at least one ε4 allele, where the presence of at least one ε4 allele was considered a carrier. For 103 subjects without APOE information, SAS 9.4® procedure PROC MI was used to impute missing values for the indicator variable based on family history of dementia. Four imputed data sets were generated; participants with two or more positive imputations for *APOE* ε4 were coded as *APOE* ε4 positive. *APOE* ε4 positivity is a major risk factor for AD-type dementia [96]. Other data collected included age at baseline, race, BMI, years of education, as well as self-reported indicators of cardiovascular disease (i.e., diabetes, hypertension, and smoking), coronary artery bypass graft (CABG), congestive heart failure, hypertensive medication, and memory change at the baseline. These data were obtained at enrollment and annually thereafter as recognized risk factors for dementia [97] .

History of significant cognitive or motor impairment due to stroke was an exclusion criterion, thus stroke was not considered in the models.

Case Ascertainment

To create a predictive model, we used clinical dementia status (dementia vs. non-dementia) at end of follow-up as the outcome. Dementia cases were identified through two methods during annual follow-up. First, as described above, a medical records-based consensus diagnosis was used. Date of diagnosis was assigned as the date of the failed screen. Second, because many participants were reluctant to obtain medical workups for their memory, additional longitudinal measures including the AD8 Dementia Screening Interview [94], self-reported medical history, self-reported diagnosis of dementia, use of memory enhancing prescription drug, and cognitive scores including the MIS, CERAD-e T Score, NYU Paragraph Delayed Recall, and TICS-m were used to identify cases. The diagnostic criteria for the second method were AD8 total of ≥ 1 (at any time during follow-up) to indicate functional impairment [94] plus one of the following: a self-reported diagnosis of dementia, use of a memory enhancing prescription drug (donepezil, rivastigmine, galantamine, or memantine), or cognitive score below cutoffs for intact cognition on any test (for example: 1.5 SDs below expected performance based on age and education normative data[95]. The date of diagnosis was assigned to the earliest event.

Data analysis

Chi-square and t-test statistics were used to examine differences in categorical and continuous variables between dementia groups. Univariate logistic regressions were performed first, and only those variables significantly associated with probability of dementia at univariate analysis would be included in the multivariable

logistic regression. Covariates included in the initial multivariable logistic regression model were age, education, smoking, APOE-ε4 allele status (any vs. none), history of hypertension, diabetes, coronary artery bypass graft (CABG), antihypertensive medication use, and memory change. In the model, age and education were used as continuous variables, and the rest were binary variables (yes vs. no). Logistic regression with backward elimination method was performed to compare with the neural network. Covariates age, education, APOE-ε4, and self-reported memory change were left in the final logistic regression model without interaction terms. In the preliminary analysis, neural network revealed an interaction effect among years of education, age at baseline, status of memory change, and APOE-ε4 allele status. The logistic regression was then conducted again to confirm the interaction effects.

Neural Network

As an extension of generalized linear models (GLM), artificial neural network (ANN) is applied to explore the complex relationship between covariates and response[143]. Multilayer perceptron (MLP) is the main model for neural network which consists of vertices and directed edges called neurons and synapses in the study respectively. Neurons are organized as layers and connected by synapses. Our ANN model had three neuron layers: input, hidden, output (See figure 4.1). The input layer included all covariates in separate neurons, and the output layer consisted of the response variable (output). The layers between input and output layers are referred as hidden layers because they are not observed. For each synapse, a weight is attached to indicate the effect of the corresponding neuron. All data will pass through the neural network as signals, and these incoming signals will be first processed by the activation function, and

then by integration function to approximate output of the neuron. Based on Hornik [144], one hidden layer is sufficient, two or more hidden layer may be needed in some circumstance. An MLP with one hidden layer consisting of J hidden neurons can be represented by the following function:

$$y \approx g\left(\omega_0 + W^T \left\{f\left(\omega_{0j} + \sum_{i=1}^{n} \omega_{ij} x_i\right)\right\}_{j=1}^{J}\right),$$

$$= g\left(f\left(\omega_{0j} + W_j^T x\right)\right),$$

where y stands for output, ω_0 indicates the intercept helping define the output neuron and ω_{0j} indicates the intercept helping define the *j*th hidden neuron. $W_j^T = (\omega_{1j}, \ldots, \omega_{nj})$, which indicates the vector of weights corresponding to the synapses from input and leading to the *j*th hidden neuron, and $x = (x_1, \ldots, x_n)$ denotes the vector of all covariates.

The function g above denotes the integration function and is defined as

$$g(z) = z.$$

The function f denotes the activation function to calculate z in the above formula. Here, the logistic function is used: $(f(u) = \frac{1}{1+e^{-u}})$.

Then supervised learning is applied in which true output is defined and is compared to the predicted output. The starting weights are usually assigned randomly from the standard normal distribution[143]. Weights are also chosen at this stage[145]. To fit the neural network, the following steps are repeated:

1) Neural network calculates a predicted output o(x) for given inputs x and starting weights.
2) An error function E, for example, sum of squared errors (SSE)

$$E = \frac{1}{2}\sum_{l=1}^{L}\sum_{h=1}^{H}(o_{lh} - y_{lh})^2$$

or the cross-entropy

$E = -\sum_{l=1}^{L}\sum_{h=1}^{H}(y_{lh}\log(o_{lh}) + (1 - y_{lh})\log(1 - o_{lh}))$, where l = 1,…, L indicates the observations, h = 1,…,H the output nodes, lh = hth nodes for lth observation,

will be applied to measure the difference between the actual output and predicted output.

3) Then all weights are adapted based on the rule of a learning algorithm.

The process will stop if the pre-specified criterion (rule of a learning algorithm) is reached, for example, all components of the gradient vector of the error function with respect to the weights ($\partial E/\partial \boldsymbol{w}$) are smaller in absolute value than a given threshold or a specified maximum step (it is referred as number of iterations) is reached. The resilient backpropagation algorithm (rprop+) is the most commonly used learning algorithm [146]. Weights are modified by searching in the opposite direction of the partial derivatives until a local minimum is found [143]. Additional technical details about ANN can be found in Gilnther's technical report and Quintana's paper [143, 147].

Our ANN input layer included four covariates including age, education, APOE-ε4, and self-reported memory change, in order to be directly comparable to the logistic regression model. We decided to have 10 hidden units based on the consideration based on literature[148]. The output layer had one neuron, which was dementia status at end of follow-up. Logistic was used as the activation function since the outcome was binary. Since cross entropy did not work with the data, and as indicated by Hastie in Section

2.3.1[148], it is not unreasonable to use identity function in binary outcome, so identity function was applied as integration function, and sum square error was calculated. The "rprop+" algorithm was used to determine the weights. AUC was calculated to compare the performance between logistic regression and ANN on classification of dementia status.

Descriptive analysis and logistic regression were conducted by using SAS 9.4® (SAS Institute, Inc., Cary, NC). ANN was performed in R package "Neuralnet" under R (R Foundation for Statistical Computing, Vienna, Austria, version 3.1.2) [149]. Statistical significance was set at $p < 0.05$.

RESULTS

Table 4.1 presents the general characteristics of participants in both RCT and central follow up. Of 3784 subjects, 277 had been diagnosed with dementia at the end of follow-up. Compared to subjects who did not develop dementia, subjects who developed dementia were older at baseline, less educated, were more often smokers, carried the *APOE*-ε4 allele, used antihypertensive medication, and reported experiencing a memory change at baseline (Table 4.1).

Based on preliminary analysis (data not shown), the prediction error in the neural network did not change dramatically as the threshold of the partial derivatives of the error function changed; we chose 0.1 as the threshold. Figure 4.1 depicts the neural network structure for the current study and shows the final weights of the corresponding synapses. These weights were used to calculate the estimated probability of the response variable. To interepret the association found in the neural network, the estimated probabilities of having dementia for 36 hypothetical subjects are presented in Table 4.2. The measure of

association for having dementia given a certain covariate in the neural network depends on the covariate and other covariates in the model. From Table 4.2, keeping other covariates in the model constant, as age increased, the estimated probability of having dementia is increased. For example, for subjects 1, 2 , and 3, who represent persons who are non-APOE- ε4 carriers, have no self-reported memory change, and have 17.8 years of education (1 standard deviation (SD) above average) and are aged at 62.2 years (1 SD below the average), at 67.2 years (average), and at 72.2 years (1 SD above the average), respectively, the estimated probabilities of developing dementia are 0.029, 0.052, and 0.068, respectively. Similarly, we can conclude APOE-ε4 allele is associated with increased esitmated probability of dementia.

As illustrated in Table 4.2, the effect of education on risk of dementia depended on age, APOE-ε4 allele status, and status of memory change. Higher education was associated with lower risk of dementia only in younger subjects, but not in younger subjects with APOE-ε4 and memory change. For example, in the younger age group (1 SD below the mean age), the estimated probability ($\hat{p}$ = 0.003) of having dementia for hypothetical subject 7 with one SD above the average for education is much lower than subject 1 ($\hat{p}$ = 0.029) with one SD below average education. Similar comparisons can be made for subjects 10 ($\hat{p}$ = 0.054) and 16 ($\hat{p}$ = 0.002), but not for subject 28 ($\hat{p}$ = 0.070) and subject 34 ($\hat{p}$ = 0.098), who are hypothetical subjects with both APOE- ε4 and memory change. Education did not have a protective effect on risk of dementia for older subjects (1 SD above mean age), especially for older subjects with APOE-ε4 and memory change. No matter what education levels were, older subjects who were APOE- ε4 carriers and had memory changes had the highest risk of dementia, such as subjects 30 ($\hat{p}$

= 0.354), 33 ($\hat{p}$ = 0.364), and 36 ($\hat{p}$ = 0.372) . In contrast, well-educated younger subjects who did not have either APOE-ε4 or memory changes had the lowest risk of dementia, such as subject 7 ($\hat{p}$ = 0.003), subject 16 ($\hat{p}$ = 0.002), subject 25 ($\hat{p}$ = 0.001).

According to the results in neural network in which the effect of education interacted with age, status of *APOE*-ε4, and status of memory change, logistic regression were performed to confirm the interaction effects. Table 4.3 shows parameter estimates and p values for each 3-way interaction regression model. Education in years interacted with *APOE*-ε4 allele carrier, and self-reported memory changes are significantly associated with having dementia (p = 0.01). To demonstrate the effect modification identified in the logistic regression model, 36 hypothetical subjects are presented in table 4.4. Subjects with no APOE- ε4 and memory change had highest estimated probability of having dementia, such as subject 30 ($\hat{p} = 0.664$), and subject 33 ($\hat{p} = 0.594$). Age modified the effect of education; however, comparing subjects 28, 29, 30, or subjects 19, 20, 21 from table 4.4, the interaction effect among age education, *APOE- ε4* and memory change is not significant. Furthermore, *APOE- ε4* status had a stronger association with dementia in future than the effect of memory change when comparing subject 12 ($\hat{p} = 0.315$) to subject 21 ($\hat{p} = 0.164$), and subject 11($\hat{p} = 0.205$) to subject 20($\hat{p} = 0.125$), and so on.

Comparison of overall performance between logistic regression and ANN for predicting incident dementia was recorded in Table 4.5. ANN had slightly better predictive accuracy than logistic regression (AUC in neural network = 0.732 vs. AUC in logistic regression 0.725). Overall, neural network has better in sensitivity (83.2%) and negative predictive value (98.0%) than sensitivity (73.6%) and negative predictive value

(97.2%) in logistic regression, but worse in the positive predictive value (10.0% in neural network vs. 41.4% in logistic regression).

DISCUSSION

The purpose of this study was to compare predictive accuracy for incident dementia between neural network and logistic regression in the PREADViSE trial. Neural network showed slightly improved predictive accuracy (AUC = 0.732) compared in logistic regression (AUC = 0.725). The model obtained from the neural network had slightly better sensitivity and negative predict value, but worse in positive predictive value. Similar association between covariates and the outcome were found in neural network and logistic regression, but the model in neural network is more difficult to interpret than logistic regression. Furthermore, neural network can easily identify more complex relationships among model variables, here education and age, APOE, and self-reported memory change. While higher education is usually considered universally protective against dementia [150, 151], the effect of education on dementia in the neural network depended on age, APOE-ε4 allele status, and self-reported memory change.

Stephan et al[45] evaluated predictive accuracy of dementia prediction models and found that poor predictive accuracy is associated with single-factor models, long follow-up intervals, and all-cause dementia for outcome ascertainment, which assumes all dementias share risk factors. The Canadian Study of Health and Aging (CSHA) [152] showed lower predictive accuracy (AUC = 0.77 in 10-year follow-up than 5 –year follow up (AUC = 0.83). The predictive accuracy (AUC = 0.732) in our neural network model is slightly lower than the CSHA 10-year study, but is comparable to the Gothenburg H-70 1902-02 birth cohort for 10-years of follow-up (AUC = 0.74)[153]. In contrast to the CSHA

study, Exalto et al did not find any significantly different results on predictive accuracy in two Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) studies based on follow-up time (one is 10 years follow-up and another one is 36 years)[59, 154]. Follow-up time in the current study was over 10 years.

Based on covariates used to generate the predictive model, models generated in the previous papers can be summarized into the following categories: 1) demographic only model; (2) cognitive tests based models with or without demographic data; (3) comorbidity data model; (4) genetic and biomarker model; (5) models including demographics, comorbidities, genetics, and biomarkers. Our logistic regression model included age, education, APOE, and memory changes to predict incident dementia and had moderate predictive accuracy (AUC: 0.725, sensitivity 73.6% and specificity 60.7%). Another similar study [154]in which the model was derived from demographic variables, health risk factors and *APOE*, obtained slightly better diagnostic accuracy (AUC = 0.78).This study also argued that diagnostic accuracy will not change significantly after removing *APOE* from the model (AUC: 0.77; sensitivity 77% and specificity 63%). Other models include neuroimaging information and/or neuropsychological tests. Tang et al. argued in their review that genetic information and/or imaging data do not improve diagnostic accuracy significantly [46, 140]. Furthermore, predictive models using one or multiple neuropsychological tests as covariates seem to have higher predictive accuracy, but there is not direct comparison for these two approaches due to between-study variation, such as different criteria on outcome measurement[45]. Waite and colleagues argued that refining the subgroups of dementia types may improve diagnostic accuracy,

but is unlikely to be cost effective because defining these subgroup of dementia can be expensive[155].

On the other hand, from machine learning and classical statistical methods, neural network in several studies has demonstrated superior ability to identify complex relationships in data compared to classical statistical methods[156, 157]. Also, neural networks obtained higher predictive accuracy rate than linear discriminant analysis and successfully distinguished Alzheimer's patients from control aged 80 years and older in the Nun study using neurofibrillary tangles and neurotic plagues counts (AUC was not reported) [158]. In contrast, Maroco et al.[159] suggested that random forest and linear discriminant analysis performed better than other statistical methods, such as neural network, support vector machines, and logistic regression based on the consideration of predictive accuracy, sensitivity, specificity. They also argued that neural networks and logistic regression are inappropriate for unbalanced data, which means small frequency vs. large frequency group in response variable[160-163].

Furthermore, Song et al. [164] compared the machine learning methods with classic statistical methods for two biomedical datasets: one was from patient care records and another was from a population survey, and they did not find significant differences in prediction between the two datasets, which indicates that the quality of the questionnaire may be more important than accuracy of the answers in the questionnaire.

Strengths for this study include larger sample size and long follow-up. We were also able to consider most well-established risk factors for dementia, including demographic, genetic, and medical characteristics, including cardiovascular risk factors. This study also had some limitations. Our outcome diagnosis was based on two criteria

due to lack of medical records from many participants, our case ascertainment may be less accurate. However, misclassification of diagnosis is independent of exposure measurement, so no differential misclassification is unlikely. Thus, results are likely biased toward the null.

In conclusion, neural network did not significantly improve predict accuracy over logistic regression and also increased difficulty of interpretation of the association between the outcome and covariates. The most important to improve performance of a model, does not depend on statistical methods, or computational techniques, but depends on how much accurate information the dataset contain. In future, the similar study should focus on refining the definition of outcome diagnosis, improving quality of questionnaire, performing validation after generating a risk model.

Table 4.1. General Characteristics of participants in PREADViSE

Characteristic	All Subjects (N=3784)	No Dementia (n=3557)	Dementia (n=227)	P value
Baseline age[b], y	67.2±5.0	67.0±5.0	70.1±5.2	< 0.001
Education[b], y	15.5±2.3	15.5±2.3	15.0±2.5	0.002
Black race[c]	318 (8.4)	294 (8.3)	24 (10.6)	0.22
Baseline smoking[c]	2018 (53.4)	871(52.9)	85 (61.2)	0.01
APOE-ε4 (≥1 ε4)[c]	956 (25.3)	1876 (24.5)	153 (37.4)	< 0.001
Baseline hypertension[c]	2998 (39.7)	2703 (38.6)	295 (53.4)	<0.001
Baseline diabetes[c]	354 (9.4)	322 (9.1)	32 (14.1)	0.01
Baseline BMI[ab], kg/m^2	28.4±4.3	28.4±4.3	28.4±4.5	0.93
Baseline CABG[ac]	135 (3.6)	119(3.4)	16(7.1)	0.004
Baseline Congested Heart disease[c]	18(0.5)	16(0.5)	2(0.9)	0.36
Baseline antihypertensive medication[c]	1413 (37.3)	1308(36.8)	105(46.3)	0.004
Memory change[c]	852 (22.5)	762 (21.4)	90 (39.7)	<0.001

[a]BMI: Body Mass Index; CABG: Coronary artery bypass graft;[b] mean ± standard deviation; [c]count (%).

Table 4.2. Illustration effect of education by age, APOE-ε4 allele and memory change status for hypothetical subjects from neural network

Education[b]	Age[a]					
	Old		Average		Young	
	Subject ID	$\hat{p}$[c]	Subject ID	$\hat{p}$[c]	Subjects ID	$\hat{p}$[c]
Absence of APOE- ε4 allele and Absence Memory change						
Low	3	0.068	2	0.053	1	0.029
Average	6	0.066	5	0.046	4	0.018
High	9	0.062	8	0.037	7	0.003
Presence of APOE- ε4 allele and Absence of memory change						
Low	12	0.148	11	0.103	10	0.054
Average	15	0.128	14	0.079	13	0.028
High	18	0.104	17	0.053	16	0.002
Absence of APOE- ε4 allele and Presence of memory change						
Low	21	0.145	20	0.126	19	0.091
Average	24	0.113	23	0.096	22	0.048
High	27	0.100	26	0.053	25	0.001
Presence of APOE- ε4 allele and Presence of memory change						
Low	30	0.354	29	0.056	28	0.070
Average	33	0.364	32	0.071	31	0.084
High	36	0.372	35	0.058	34	0.098

Note: Note : [a]Young = 62.2 years , Average = 67.2 years, Old = 72.2 year ; [b]Low =13.2 years of education, Average =15.5 years of education, High = 17.8 years of education; [c]$\hat{p}$ = estimated probability of having dementia

Table 4.3 Parameter estimates from interaction of logistic regression

Variables	Estimate (SE)	P value
Intercept	4.78(5.59)	0.39
Age at baseline	-0.10(0.08)	0.22
Education in years	-0.91(0.37)	0.01
Presence of *APOE*- ε4 allele	-1.91(2.11)	0.37
Presence of memory change	2.45(2.07)	0.24
Age at baseline * Presence of *APOE*- ε4 allele	0.05(0.03)	0.04
Age at baseline * education in years	0.01(0.005)	0.02
Age at baseline * Presence of memory change	-0.002(0.03)	0.91
Education in years * Presence of *APOE*- ε4 allele	-0.08(0.07)	0.30
Presence of *APOE*- ε4 allele * Presence of memory change	-4.85(1.99)	0.01
Education in years * Presence of memory change	-0.10(0.07)	0.18
Education in years *Presence of *APOE*- ε4 allele * Presence of memory change	0.32(0.13)	0.01

Table 4.4. Estimated probability of having dementia from multivariable logistic regression to illustrate interaction effects among age at baseline, education, APOE- ε4 allele and memory change

Education[b]	Age[a]					
	Old		Average		Young	
	Subject ID	$\hat{p}$[c]	Subject ID	$\hat{p}$[c]	Subjects ID	$\hat{p}$[c]
Absence of APOE- ε4 allele and Absence Memory change						
Low	3	0.059	2	0.044	1	0.032
Average	6	0.055	5	0.036	4	0.023
High	9	0.051	8	0.029	7	0.016
Presence of APOE- ε4 allele and Absence of memory change						
Low	12	0.315	11	0.205	10	0.126
Average	15	0.299	14	0.172	13	0.091
High	18	0.284	17	0.143	16	0.066
Absence of APOE- ε4 allele and Presence of memory change						
Low	21	0.164	20	0.125	19	0.095
Average	24	0.126	23	0.084	22	0.055
High	27	0.097	26	0.056	25	0.032
Presence of APOE- ε4 allele and Presence of memory change						
Low	30	0.664	29	0.525	28	0.382
Average	33	0.594	32	0.415	31	0.256
High	36	0.519	35	0.313	34	0.161

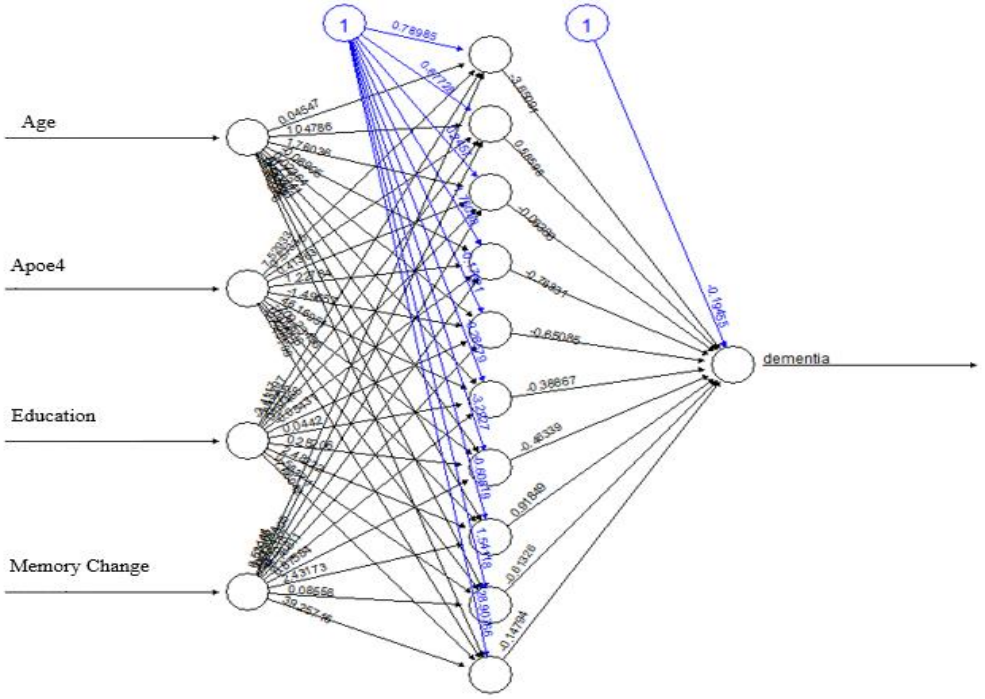
Note: Note : [a]Young = 62.2 years , Average = 67.2 years, Old = 72.2 year ; [b]Low =13.2 years of education, Average =15.5 years of education, High = 17.8 years of education; [c]$\hat{p}$ = estimated probability of having dementia

Table 4.5. Comparison of predictive performance of logistic regression and neural network

	Logistic regression[a]	Neural network[a]
Sensitivity	73.6%	83.2%
Specificity	60.7%	51.4%
Positive Predictive Value	41.4%	10.0%
Negative Predictive Value	97.2%	98.0%

Note : [a]Area under curve : 0.725 in logistic regression and 0.732 in neural network

Figure 4.1 . Graphics of neural network for incidence of dementia in PREADViSE trial. Age, *APOE-ε4*, Education, Memory Change represent the 4 input neurons on the left side of the diagram. Each input neuron was connected with 10 hidden neurons (second column of empty circles from the left of figure) by 10 corresponding synaptic weights. The 10 hidden units and the output neuron – dementia were connected by the synapses starting the hidden units and ending at the output layer. The first "1" in the circle from the left of the figure represents the intercepts of each hidden neuron, and the second "1" in the circle stands for the intercept of output neuron. These weights and intercepts were adapted to calculate the estimated probability of dementia. The model was stopped after 203313 steps, and predication error is 99.02907.



CHAPTER FIVE

Conclusion

Summary

Understanding its prevalence, risk factors, and development and potential interventions for dementia is becoming an important facet of public health and health care delivery. The purpose of this dissertation was to develop further the body of literature about risk factors, development, and prediction of dementia. Two datasets including Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADViSE trial) and Alzheimer's Disease Neuroimaging Initiative(ADNI) were used to conduct three studies: (1) "Self-reported sleep apnea and dementia risk: Findings from the PREADViSE Alzheimer's disease prevention trial;" (2) "Evaluating trajectories of episodic memory in normal cognition and mild cognitive impairment: results from ADNI;" (3) "Comparison between neural network and logistic regression in PREADViSE trial." The major findings from these studies are summarized below:

Chapter Two examined the association between self-reported sleep apnea at baseline and risk of dementia in a U.S. male population. This was the first study to investigate this topic in this population using a cohort study. Two cohort studies[82, 83] had shown that sleep apnea is significantly associated with risk of dementia in U.S. female and Taiwanese population. By contrast, a few cross-sectional studies found no association between sleep apnea and cognitive decline. One the other hand, one small cross-section study and one ADNI study suggest that the association between sleep apnea and dementia depends on the status of APOE-ε4. We demonstrated that sleep apnea in

general is not associated with risk of dementia in U S male population. However, for APOE-ε4 non-carrier, men with sleep apnea had an estimated 66% increased risk to develop dementia.

Considering longitudinal studies feature of dementia studies, Chapter Three shifts focus to the trajectory of development into dementia. Many statistical methods including linear mixed effect model, Markov processes, multi-stage disease progression model, have been applied to investigate change or trajectory of cognitive and neuropsychological measurement over time. Nagin and colleagues developed the group based trajectory model (GBTM) which accommodates the discrete nature and truncated distribution of outcome. It assumes that the sample is composed of a mixture of distinct groups, and that each group of individuals follows a similar developmental trajectory in terms of changes at mean level of outcome measurements [38-41]. Furthermore, one advantage of GBTM is that it qualitatively identifies distinct developmental groups that may not be identifiable by using LMM [42, 43]. Another advantage is that the model can distinguish real differences from chance variation. Chapter Three explored potential trajectories in episodic memory scores in normal and MCI subjects enrolled in the ADNI and assessed whether the risk factors that influence these trajectories differ by cognitive status using GBTM.

This study confirmed heterogeneity of episodic memory in both baseline normal and MCI subjects. In baseline normal subjects, 6 distinct trajectories were identified based on the baseline value of RAVLT 30 min-delayed recall and shape of trajectory during years while 5 trajectories in MCI subjects. Accounting baseline scores, the 6 group trajectories in baseline cognitive normal subjects can be summarized as three type

of trajectories: stable (Group 3 and Group 6), linear decline (Group 1 and Group 2), and curvilinear decline (Group 4 and Group 5). About a third of baseline normal subjects will remain cognitively normal over time, and about 28% of subject's present curvilinear decline. In contrast to the trajectories identified for normal subjects, all 5 trajectories group for MCI showed the tendency to decline. Over 65% subjects remained MCI throughout follow-up. Subjects with trajectories in Groups 1 and 2 were more likely to progress to dementia. The study also confirmed that disparate outcomes for MCI subjects. About 11% and 22% MCI subjects in Groups 4 and 5, respectively, were reverted back to normal cognitive states and 19% and 13% were converted to dementia, respectively. Furthermore, the study demonstrate different demographic variables were significantly associated with different trajectories in normal and MCI subjects. Age, education, BMI are significantly associated with trajectories for normal and MCI subjects. However, APOE is only significantly associated with trajectories for MCI subjects.

In Chapter Four, we aimed to compare predictive performance from parametric and non-parametric method using PREADViSE study. Two recently systematic reviews reported nearly all parametric research methods for prediction of dementia risk in the past decades [45, 46] and recommend that none of them are recommended for dementia risk prediction in the population setting due to sample selection, model diagnostics, and model validation [45, 46]. Several non-parametric methods were commonly used including classification tree, random forest, and neural network. Chapter 4 compared the performance of logistic regression and neural network and found that neural network obtains slightly improved predictive accuracy (AUC = 0.732) comparing to predictive

accuracy (AUC = 0.725) in logistic regression. Neural network obtain similar association between covariates and outcomes as logistic regression did. Moreover, neural network can demonstrate more complex relationships among covariates. Based on finding from neural network, the effect of years of education on risk of dementia depends on APOE-ε4 allele, years of age, self-reported memory change.

Strengths and limitations

A major strength of this dissertation is that two datasets used in this dissertation were drawn from two large and clinically well-defined longitudinal study with adequate follow-up time (over 11 years in PREADViSE and 9 years in ADNI study). Long –time follow-up can lead to more incident cases to increase power of survival analysis and provide adequate data points to investigate the development of dementia. Furthermore, the dissertation will enrich the body of literature about dementia from comprehensive aspects including prevention (finding risk factor of dementia, chapter 2), development (trajectory of episodic memory, chapter 3), and prediction (predictive of model of dementia, chapter 4) of dementia.

In chapter 2, survival analysis was conducted for the first time in U.S. male population for association between self-reported sleep apnea and risk of dementia. The limitation for this chapter may include missing cases or misclassification of exposure or outcome. However, use of the AD8 functional status screen demonstrated better agreement with medically-confirmed ascertainment, which improve ascertainment of cases. Based on the phrasing of questionnaire for self-reported measure of sleep apnea, it is most likely that non-differential misclassification happened, which should only lead to

the results towards null. In chapter three, we applied group trajectory based model to illustrate episodic memory trajectory in baseline cognitive normal and MCI subjects, which is semi-parametric model developed by Nagin. The model assumes that the sample is composed of a mixture of distinct groups, and that each group of individuals follows a similar developmental trajectory in terms of changes at mean level of outcome measurements [38-41]. And there are only a few paper available in the literature on how to apply and fit GBTM, which could be a better statistical methods for longitudinal dementia studies. However, GBTM has its limitation, which is that the direct relationship between outcome (dementia) and risk factors (such as age education, gender, etc) does not exist, so we cannot quantitatively interpret the association between outcomes and covariates as routine. We applied neural network, a novel statistical learning method and compared it to the logistic regression in chapter 4. The better strategy to compare neural network and logistic regression is to perform validation, then compare the predictive performance between neural network and logistic regression.

Future Research

Several avenues of future research have been suggested by the studies in the dissertation. First, replication study using objective measure of sleep apnea and consistent diagnosis of incident dementia for chapter 2 are needed to confirm the association between sleep apnea and risk of dementia. As discussed above, rigorous outcome diagnosis criteria are called to improve ascertainments of incident cases. Furthermore, measurement of sleep apnea in chapter 2 came from self-reported questionnaire which may cause non differential misclassification. Objective measure of sleep apnea such as

apnea-hypopnea index, are needed to recheck the association. Many sleep apnea subjects who were taking sleep treatments, such as Continuous Positive Airway Pressure (CPAP) therapy or pills. In future study, we also wonder whether or how much these treatments influence the association between sleep apnea and risk of dementia.

In Chapter Three, we examined the trajectory of RAVLT 30-mimtute delayed recall as index of episodic memory in normal and MCI subjects. In the future, we would assess trajectory of other test scores of RAVLT, which represent different aspects of cognitions. In additional to RAVLT, we also propose to investigate a series of trajectories of other neuropsychological tests, such as dysexecutive components using data in ADNI. Moreover, we are also interested in finding the best index whose trajectory is the most associated with conversion or progression to dementia. MCI in ADNI 1 were generally defined and it was not determined the specific stage or time of MCI. In ADNGO, and ADNI2, two specific group MCI subjects: early MCI and later MCI were recruited, it will be interesting to study the specific trajectories for these subpopulation.

Appendix

Table 1s: Mean and Standard deviation of 30 min delayed recall of RAVLT baseline at each follow-up assessment

	Month	Normal							MCI					
		Overall (n)	Group 1 (n)	Group 2 (n)	Group 3 (n)	Group 4 (n)	Group 5 (n)	Group 6 (n)	Overall (N)	Group 1 (n)	Group 2 (n)	Group 3 (n)	Group 4 (n)	Group 5 (n)
RAVLT	0	7.4±3.7(217)	3.3±1.8(33)	6.2±2.7(58)	6.9±3.0(42)	9.4±3.1(31)	9.1±2.2(30)	12.9±2.3(22)	2.9 ±3.3(371)	1.5±1.6(143)	0±0(66)	3.3±1.9(66)	5.6±3.0(73)	10.1±3.2(23)
	6	6.9±3.5(215)	2.5±1.8(30)	4.7±2.0(58)	7.4±2.1(44)	9.4±2.2(31)	8.5±2.1(30)	11.9±2.8(22)	2.3±3.1(367)	0.8±0.9(143)	0±0(65)	2.6±1.9(64)	4.6±2.7(72)	10.0±2.7(23)
	12	7.9±3.7(208)	3.5±2.2(30)	6.0±2.3(52)	7.6±2.7(44)	10.5±2.2(31)	9.2±2.2(30)	13.6±1.4(21)	2.4±3.5(347)	0.5±0.8(138)	0±0(57)	2.7±1.8(62)	5.2±3.0(67)	11.4±2.3(23)
	18[a]	-	-	-	-	-	-	-	2.1±3.1(315)	0.4±0.7(122)	0±0(52)	1.8±1.7(57)	5.2±2.7(64)	9.2±2.7(20)
	24	8.1±4.0(199)	2.8±2.6(29)	6.1±2.2(51)	7.8±2.3(40)	11.7±1.6(30)	9.8±2.5(29)	13.4±3.0(20)	2.3±3.5(289)	0.3±0.7(114)	0±0(44)	2.3±1.9(55)	5.1±3.0(55)	11.0±2.8(21)
	36	6.8±3.7 (183)	1.4±1.7(24)	4.2±1.9(45)	7.6±1.6(38)	10.0±1.9(28)	7.8±1.6(29)	12.3±2.4(19)	2.2±3.4(243)	0.2±0.5(86)	0.2±0.4(32)	1.5±1.5(52)	4.3±2.4(53)	10.5±3.5(20)
	48	7.5±4.3(120)	2.0±1.9(15)	4.3±2.6(28)	7.8±2.9(29)	11.4±1.6(18)	7.7±2.1(18)	14.4±1.0(12)	2.1±3.3(141)	0.1±0.4(46)	0.1±0.4(20)	1.7±1.7(34)	4.7±2.9(30)	8.6±4.3(11)
	60	6.9±4.4(106)	1.6±1.6(13)	3.8±2.6(23)	7.0±2.4(27)	10.1±2.9(19)	6.6±3.6(13)	14.1±1.4(11)	2.4±3.8(106)	0.1±0.2(31)	0±0(12)	1.0±1.5(28)	4.7±2.8(25)	11.2±3.6(10)
	72	7.1±4.5(110)	1.0±1.4(12)	4.2±2.1(24)	7.8±2.5(25)	10.8±2.0(19)	4.9±3.1(18)	14.6±0.9(12)	2.7±4.1(101)	0.1±0.3(27)	0.1±0.3(11)	1.2±1.3(24)	4.2±3.6(27)	11.2±3.6(12)
	84	7.4±4.5(95)	1.4±1.9(9)	3.4±2.5(17)	7.7±2.2(23)	10.5±2.4(18)	5.1±3.1(15)	14.2±1.0(13)	2.6±3.8(75)	0±0(17)	0±0(6)	1.3±1.3(20)	3.5±2.7(21)	8.8±5.3(11)
	96	5.8±4.7(63)	0.4±0.9(5)	3.1±1.7(14)	7.9±2.1(15)	9.6±2.9(10)	1.5±2.2(13)	14.3±0.8(6)	2.2±3.2(54)	0.1±0.3(11)	0±0(4)	0.8±1.4(11)	3.7±2.9(21)	5.0±5.1(7)
	108[b]	5.8±5.1(13)	6.0±0(1)	4.5±2.1(2)	10.3±2.9(3)	7.0±2.8(2)	0±0(4)	15±0(1)	4.1±5.3(10)	0±0(3)	-	-	5.2±3.8(5)	7.5±10.6(2)

Note: [a] Baseline normal subjects were not assessed in 18 months; [b]None of MCI subjects in group 1 and group2 were assessed at 108 month

Figure 1s. Model based trajectories overlaid with crude trajectories for normal ADNI subjects. Solid lines indicate model based trajectories and dash lines stand for crude trajectories. The model based trajectories show discrepancy with crude trajectories at the end points of follow up.

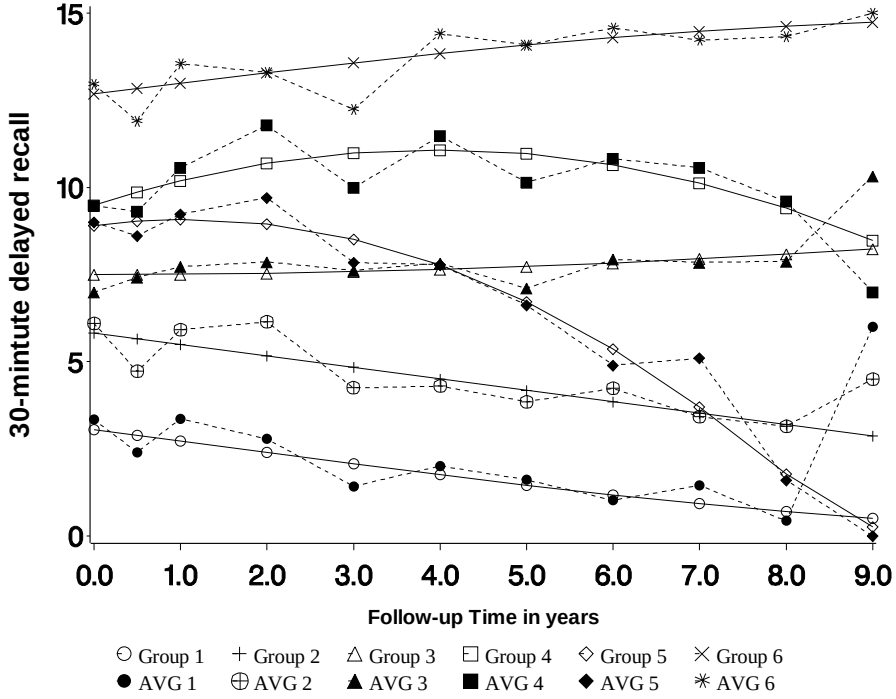
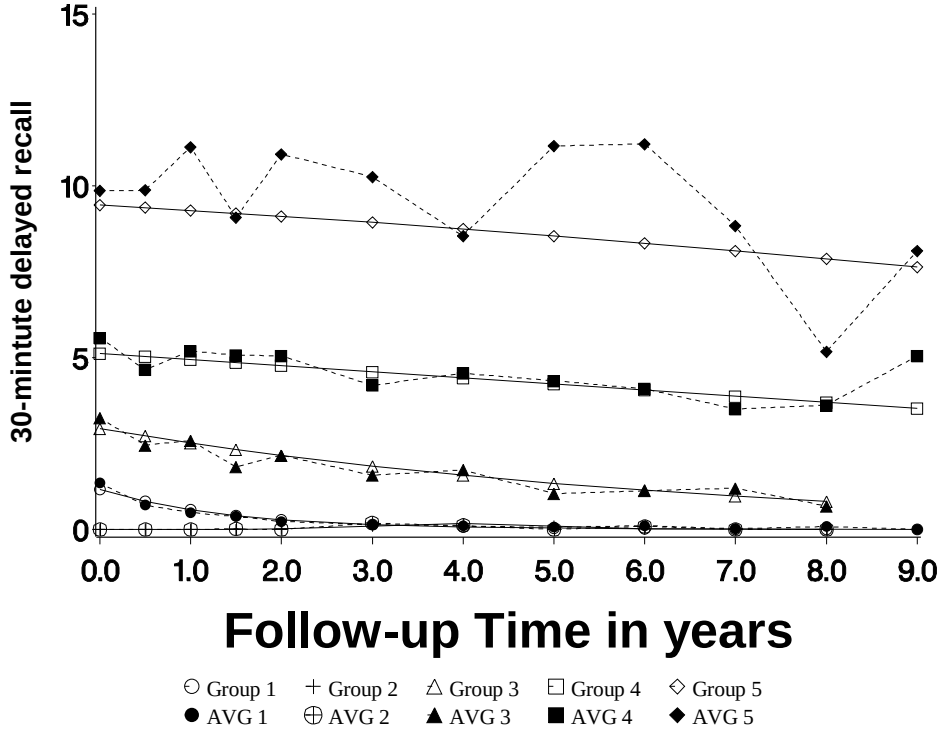


Figure 2s. Model based trajectories overlaid with crude trajectories for MCI ADNI subjects. Solid lines indicate model based trajectories and dash lines stand for crude trajectories. The model based and crude trajectories demonstrate good match for Group1-4, but not in Group 5, which may be due to less participants in that group and/or mean- variance relationship (larger mean goes with large variance) in ZIP distribution.



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