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Using Data and Evidence to Improve Quality of Life for Patients with Alzheimer's Disease

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Ying Wang

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Abstract

Using Data and Evidence to Improve Quality of Life for Patients with Alzheimer's Disease

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As an irreversible, progressive brain disorder, Alzheimer's disease (AD) imposes a severe burden upon patients and their caregivers, as well as the healthcare system. Of the ten leading causes of death in the United States, Alzheimer's disease is the only one without a pharmacological intervention that has been proven to cure or delay the onset of the disease. Aging is the primary risk factor contributing to Alzheimer's disease in the elderly. With an aging population that continues to grow, the challenges for the healthcare system surrounding AD become more and more serious. My dissertation aims to contribute to a better understanding of this rising problem from big data analytics point of view. A large-scale national clinical and administrative data warehouse in the Veteran Affairs healthcare system will be used for the following investigation.

Chapter 2 investigated whether the combined therapy of four classes of low-cost FDA-approved medications targeting modifiable risk factors for AD can extend patients' lifespans with machine learning techniques. As multiple comorbidities are often present simultaneously in elderly patients, and their treatment typically involves the use of multiple medications, it is essential to investigate the comparative effects of commonly prescribed medications and their combinations on the development of Alzheimer's disease. Chapter 2 specifically focuses on the concurrent utilization of medications that belong to up to three distinct categories that have not been previously explored. This knowledge can inform the development of treatment plans that optimize the balance between managing multiple chronic conditions, minimizing the risk of developing Alzheimer's disease, and offering a potentially significant opportunity to reduce the economic burden of the disease.

Chapter 3 studied the AD disease progression and the effect of therapeutic interventions for the modifiable risk factors at each stage of AD. The disease progression of AD is a dynamic process and precise prediction of the time course is difficult. Starting from the early phase of mild cognitive impairment (MCI) to AD, then to death, the transition rates and probabilities between different disease phases were presented using the Markov multi-state modeling. Acquiring this knowledge is a critical step toward preventing and diagnosing AD at an early stage and may present opportunities for improved clinical management. Risk factors that facilitate the progression from MCI to AD were identified using Cox regression with propensity score weights. The understanding of the disease progression of AD will

contribute to the estimate of the costs related to AD, and understand the cost-effectiveness of AD-related treatments and services.

Chapter 4 aims to assess the robustness of multi-state survival models when confronted with a noisy dependent variable, particularly in the context of complex diagnostic tasks. In healthcare systems, diagnostic challenges are commonplace, often leading to missed, delayed, or erroneous diagnoses. Diseases such as Alzheimer's disease pose additional complexities, resulting in elevated diagnostic errors due to the disease's intricacies and the limited use of advanced measurements in primary care practices. Regrettably, the existing literature on algorithm performance in highly noisy data environments remains limited. In this study, I compared the classic Markov multi-state model and a deep-learning model, multi-state ODEs, utilizing simulated data with a highly noisy dependent variable. The primary goal is to discern the sensitivity of prediction outcomes from multi-state survival models for disease progression analysis. Through this investigation, our findings contribute to a better understanding of the performance of these models under challenging conditions, shedding light on their reliability and applicability in noisy data scenarios.

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Chapter 1

Introduction

1.1 The burden of Alzheimer's disease – High spending but no cure!

As an irreversible progressive brain disorder, Alzheimer's disease (AD) imposes a severe burden upon patients, their caregivers, and the healthcare system. According to statistics from Alzheimer's Association, the costs of Alzheimer's care to Medicare and Medicaid top heart cancer and heart disease as the most expensive disease in America. [1]

The direct cost of caring for those with Alzheimer's and other dementia was estimated at $305 billion. The average total cost per patient over the last five years of life reached $287,038, including around $86,430 in Medicare costs, $35,346 in Medicaid costs, $61,522 out-of-pocket spending, and $83,022 informal care costs (Kelley et al., 2015). The out-of-pocket spending for seniors with Alzheimer's and other dementia is 2.13 times higher than for patients with cancer, and 1.74 times higher for patients with heart disease. The average

[1] Fact Sheet Costs of Alzheimer's to Medicare and Medicaid, from Alzheimer's association: https://act.alz.org/site/DocServer/2012_Costs_Fact_Sheet_version_2.pdf?docID=7161

annual costs of Medicare and Medicaid for seniors with Alzheimer's and other dementia ($26,092) are more than three times higher than seniors without Alzheimer's and other dementia ($8,124). Aging is the primary risk factor contributing to Alzheimer's disease in the elderly. With an aging population that continues to grow, the challenges for American society and families surrounding AD become increasingly serious.

The tragedy of Alzheimer's patients is far beyond the high costs imposed on the family and society. Depending on the disease progression, patients with Alzheimer's gradually lose their memory and ultimately, their entire identity and the ability to care for themselves. Of the ten leading causes of death in the United States, it is the only one without a pharmacological intervention that has been proven to cure the disease. Therefore, patients with Alzheimer's spend a lot on care. The direct costs of care for Alzheimer's disease are mostly attributed to skilled nursing care, home healthcare, and hospice care. The indirect cost of care, such as improving quality of life, is likely underestimated (Wong, 2020).

1.2 Research Aims and Contributions

My dissertation seeks to enhance comprehension of the escalating issue within the healthcare system triggered by Alzheimer's disease. In contrast to conventional methodologies in medical research, such as fundamental (experimental) or clinical investigations, this research delved into three interconnected subjects using the analytical framework and argescale administrative datasets.

Paper 1: What prescription medications commonly taken by elderly individuals to manage chronic conditions are more likely to reduce the risk of developing Alzheimer's disease?

As multiple comorbidities are often present simultaneously in elderly patients, and their treatment typically involves the use of multiple medications, it is essential to investigate

the comparative effects of commonly prescribed medications and their combinations on the development of Alzheimer's disease. By investigating whether the combined therapy of four classes of low-cost FDA-approved medications targeting modifiable risk factors for AD can extend patients' lifespans with machine learning techniques, paper 1 identified the promising medication combinations. This knowledge can inform the development of treatment plans that optimize the balance between managing multiple chronic conditions, minimizing the risk of developing Alzheimer's disease, and offering a potentially significant opportunity to reduce the economic burden of the disease.

Paper 1 contributes to the advancement of knowledge on the comparative efficacy of multiple medications and their combinations in delaying the risk of AD onset. It specifically focuses on the concurrent utilization of medications that belong to up to three distinct categories that have not been previously explored. The findings provide valuable insights into potential therapeutic interventions for delaying the onset of AD. Additionally, the present study employs machine learning techniques to advance drug repositioning development for Alzheimer's disease with affordable medications using healthcare administrative data. This approach represents an innovative application of ML techniques to address a complex challenge, with the objective of identifying novel therapeutic avenues for managing the disease.

Paper 2: Estimating rates of diagnostic transition from mild cognitive impairment through Alzheimer's disease to death: Evidence of slowing the AD progression by managing modifiable risk factors with FDA- approved medications

Disease progression of AD is a dynamic process and precise prediction of the time course is difficult. Previous works revealed a large difference in the transition probability from MCI to AD due to characteristics of the study cohort, sample size, the definition of MCI, and methodological approach, and the number of inquiries that have sought to estimate such transitions throughout the entire disease continuum is restricted. By modeling the clinical disease progression of AD with an advanced Multistate Markov approach, paper

2 contributes to: 1) estimating the transition probabilities between disease stages (Mild Cognitive Impairment (MCI), AD, and Death) and determining the duration of stay at each stage, utilizing extensive longitudinal data; 2) identifying and assessing the potential medications for the modifiable risk factors of AD that may contribute to disease progression along the disease trajectory. Acquiring this knowledge is a critical step toward preventing and diagnosing AD at an early stage and may present opportunities for improved clinical management.

Paper 3: Multi-state survival model with noisy healthcare survival data

Missed, delayed, or wrong diagnoses are inevitable in the healthcare system, especially in the primary care setting where a high volume of diagnostic decisions was made in a complex and uncertain environment. Diseases like Alzheimer's appear to have higher diagnostic errors due to the complication of the disease and the limited use of advanced measurements in primary care practices. As such, improving the understanding of algorithmic performance in a highly noisy environment is crucial. However, the related discussion in the literature is limited. By exploring the multi-state survival modeling methodologies, such as the Markov model and deep learning-based models utilizing Neural ODEs, in handling scenarios with high diagnostic error rates, paper 3 offers a comprehensive view of these models in terms of feasibility, performance, and robustness under various simulated scenarios of diagnostic errors.

Overall, my research aims to provide valuable insights to businesses and healthcare organizations on how to effectively manage the impact of Alzheimer's disease on patients and the healthcare system, reducing costs and improving the quality of life for all involved.

Chapter 2

What prescription medications commonly taken by elderly individuals to manage chronic conditions are more likely to reduce the risk of developing Alzheimer's disease?[1]

2.1 Introduction

The recent approval of the Alzheimer's disease (AD) drug Leqembi by the Food and Drug Administration (FDA) provides a new therapy for the treatment of AD (Van Dyck et al., 2023). Compared to the general guideline for the appropriate use of Leqembi (Cummings et al., 2023), the inclusion criteria for use of this drug recommended by the Department of Veterans Affairs (VA) include patients aged 65 years or older with mild cognitive impairment (MCI) or mild AD. Comorbidities that include hypertension, hyperlipidemia, and diabetes are common among these patients, who are often prescribed one, two, or three medications belonging to the categories of angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), Beta Blockers, Statins, and Metformin. It is highly

[1] This chapter is published in Wang, Y., Li, M., Kazis, L. E., & Xia, W. (2023). The Comparative Effectiveness of Monotherapy and Combination Therapies: Impact of Angiotensin Receptor Blockers on the Onset of Alzheimer's Disease. JAR life, 12, 35.

significant to explore potentials of these medications to delay the clinical onset of AD and provide a window of opportunity for therapeutic intervention, regardless of the eligibility of these patients for Leqembi. These drugs are added to various medications postulated as candidate treatments for AD (Ballard et al., 2020; Bhat et al., 2021). Currently, more than 30 FDA-approved drugs for other indications are selected in preclinical or clinical investigations for use as AD therapies (Fang et al., 2020).

Patients diagnosed with AD often exhibit a wide range of comorbid diseases such as diabetes, hypertension, or hypercholesterolemia (Bunn et al., 2014). Many of these comorbid conditions related to AD have been well-recognized as modifiable risk factors for the onset of AD (Litke et al., 2021). The renin-angiotensin system (RAS)-acting antihypertensive ARB and ACEI, Beta Blockers, Metformin, and Statin are all approved by the FDA and therefore commonly used concomitantly by patients with comorbidities. A growing body of observational studies shows that selected conventional medications for the treatment and prevention of common AD comorbidities may play a useful role in prolonging the presymptomatic stage of the occurrence of AD. The solo use of ARB (Li et al., 2010; Chiu et al., 2014; Oscanoa et al., 2021), ACEI (de Oliveira et al., 2018), Statins (Wolozin et al., 2007; Jeong et al., 2021), Beta Blockers (Rosenberg et al., 2008), and anti-diabetic Metformin (Li et al., 2012) were extensively explored for their association with the reduction of the risk of AD. Although the concomitant use of medications for controlling multiple comorbidities is highly prevalent among patients with AD, limited research has been conducted to examine the associations between the concomitant use of these medications and the clinical onset of AD.

Previous studies regarding the concomitant use of FDA-approved drugs on the occurrence of AD found that the concomitant use of Statin and RAS-acting antihypertensive drugs, particularly ARBs, was associated with a reduced risk of AD and related dementia than concomitant use of Statins and non-RAS-acting antihypertensives (Barthold et al., 2020).

Our earlier study reported that the prescription of Statins and ACEI together significantly reduced the risk of developing AD in patients with a history of traumatic brain injury (TBI) (Li et al., 2020). However, the concomitant use of three medications, which is commonly observed among the elderly population, lacks thorough discussion. The current study addresses this inquiry by examining a data repository comprising electronic medical records sourced from 25 million individuals within the VA Healthcare System.

Due to many of those comorbid conditions being highly correlated with one another, the concurrent use of medications for those comorbid conditions is common among the elderly (Mancia et al., 2019). For example, clinical guidelines suggest the utilization of concomitant medications as an initial approach to attain improved management of blood pressure (Mancia et al., 2019). The class of antihypertensive agents known as ARBs is extensively employed to manage hypertension, whereas statins are employed to manage hypercholesterolemia. Approximately 25% of adults age 65 and above use antihypertensive agents and Statins concomitantly (Barthold et al., 2020). The concomitant use of ARB and Statin drugs has been postulated to have the potential for therapeutic applications in those with metabolic syndrome, type 2 diabetes, stroke, and heart failure (Nickenig, 2004). Concomitant use of multiple medications with distinct underlying mechanisms has the potential to enhance the efficacy of drug repositioning through synergistic effects, as well as delay or reduction in the development of drug resistance (Sun et al., 2016). For this reason, it is imperative to conduct a comprehensive evaluation of the concurrent use of multiple medications to examine the extent of their favorable impact on the first occurrence of AD.

The high prevalence of concomitant use of medications among patients with AD provides a unique opportunity for exploring the associations of medications and their association with the delayed onset of AD. Previous studies regarding the concomitant use of FDA-approved drugs on the occurrence of AD found that the concomitant use of Statin and RAS-acting antihypertensives, particularly ARBs, was associated with a reduced risk of AD and related

dementia than concomitant use of Statins and non-RAS-acting antihypertensives (Barthold et al., 2020). Our earlier study reported that the prescription of Statins and ACEI together significantly reduced the risk of developing AD in patients with a history of traumatic brain injury (TBI) (Li et al., 2020). This study advances our understanding of the relative effectiveness of various medications and their combinations, with a particular focus on the concomitant use of medications involving up to three different classes, an area that has not been previously explored. The objective of this study is to utilize claims data obtained from a large population-based cohort to assess and compare the effectiveness of different combination therapies consisting of one, two, or three FDA-approved drugs commonly prescribed to the elderly population (ARB, ACEI, Beta Blocker, Metformin, and Statins) in delaying the onset of Alzheimer's disease (AD).

2.2 Method

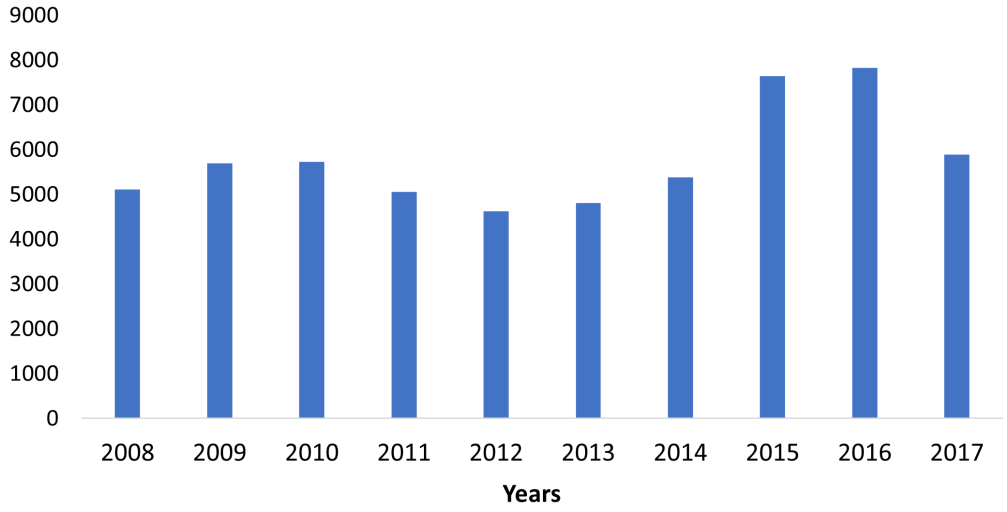
2.2.1 Study design

This is a retrospective matched case-control study with survival endpoints. The aim of this study is to evaluate the comparative effectiveness of mono and combined therapies for delaying the occurrence of the clinical onset of AD. In the doubly robust propensity score weighted Cox model, we compared the hazard risk of the clinical onset of AD in individuals with the prescription of mono-or combined therapies of ACEI, ARB, Beta Blocker, Metformin, or Statins versus those without prescription of the above therapies. In the random forest model, we applied the permutation importance approach to evaluate the relative importance of these therapies in predicting the clinical onset of AD.

2.2.2 Study population

Patient health records were obtained from the Department of Veterans Affairs (VA) national corporate data warehouse (VA-CDW) database. This included inpatient and outpatient visits, vital status, and patients' prescriptions during the study period from October 1, 1998, to April 1, 2018. We only include patients whose ages were ≥ 65 and < 90 years old at the end of the study period. Patients with AD were identified using ICD-9 and -10 diagnosis codes (Quan et al., 2008), which are standardized medical codes for the classification of diseases and medical conditions. Subjects who received at least two AD outpatient visits or one inpatient diagnosis (ICD-9 (331.0) and ICD-10 (G30.x) codes) were defined as AD patients with the first date of an AD diagnosis as the date of AD onset. The control or comparator group was a random sampling of 10% of the subjects with records in VA Informatics and Computing Infrastructure (VINCI) without a claims diagnosis of AD during the study period.

Figure 2.1: Dementia patients with possible AD from 2008 to 2017



From 1,660,151 VA patients, we identified 73,605 dementia patients with possible AD based on ICD9/10 codes. Similar incidence of AD was observed across ten years, except for year 2015 and 2016 when an elevation of AD patients was observed, possibly due to the transition of ICD-9 code to ICD-10 code on October 1, 2015.

2.2.3 Medication prescription and adherence

We collected patients'medication prescription data for ACEI, ARB, Beta Blocker, Statin, and Metformin from the same database (Fig 1). "Users of medication(s)" in this paper were defined as the patients with the following two criteria: 1) those who initiated the use of any of the target medications before the first diagnosis of AD, or before the censoring date in the case of the control group; 2) those who adhered to the treatment with the class-level medication possession ratio (MPR) of more than 0.80. Among qualified medication users, we analyzed single medication users and users with concomitant use of two or three medications. "Single medication users" were defined as those who used only one of the target medication classes during the study period. The "Users with concomitant use of two or three medications" were those who concomitantly prescribed the combined therapy for more than 90 days during the study period.

The prescription of both ACEI and ARB is not recommended in clinical practice as this combination has been postulated to have a high risk of adverse renal outcomes (Misra and Stevermer, 2009). Consistent with the recommendation, a limited number of patients (68 non-AD patients and 2 AD patients) who had a prescription of both ACEI and ARB during the study period of 20 years was identified. These patients were excluded from this study.

The average number of patients prescribed at least two classes of medications from the class of ARB, ACEI, Beta Blocker, Metformin, and Statin was 170,957 per year within the VA healthcare system. On average, more than 17% of patients have been prescribed at least two classes of medications each year (Fig 2.1).

2.2.4 Demographics and Covariates

Patients'demographic characteristics (age, sex, race/ethnicity), and comorbidities related to mental health and other health conditions were included as covariates to adjust for possible confounding effects (Helzner et al., 2008; Burke et al., 2018). The information on comor-

bidities was extracted from inpatient and outpatient visits with one ICD9/10 code and from prescription records between October 1, 1998, and April 1, 2018.

Mental health comorbidities included anxiety, bipolar disorder, schizophrenia, posttraumatic stress disorder (PTSD), depression, and substance use disorders (Table 2.1). Medical comorbidities included diabetes, sleep disorder, thyroid disorder, cardiac dysrhythmia, cancer, chronic heart failure, coronary artery disease, hyperlipidemia, hypertension, liver disease, lung disease, and renal failure (Table 2.1).

2.2.5 Statistical Analysis

Cox proportional hazard models with and without a doubly robust method with propensity score weighting (PSW) were used to assess the association of the different medication combinations with patients'pre-symptomatic survival time to the occurrence of AD (Cox, 1972; Walker and Duncan, 1967). The selection of propensity weighting (PSW) approach combined with traditional covariate adjustment is based on the fact that PSW preserves data from all participants in the study and is straightforward to implement (Elze et al., 2017). The PSW creates a pseudo population with perfect covariate balance (Elze et al., 2017). In our study, the pre-symptomatic survival time of AD onset was defined as the time from 65 years to the first AD diagnosis. The PSW approach was introduced to adjust for the potential confounding of baseline demographic characteristics among different medication user groups.

Our primary independent variable for evaluation is each different medication user group. Both demographics and comorbidities were included in all models as covariates (Table 2.1). Statistical significance was set at a level of 0.05, and maximum likelihood estimation was used to obtain the hazard ratio (HR) with 95% confidence intervals (CI). When comparing the two groups, if the two HRs have non-overlapping confidence intervals, they are significantly different at the level of 0.05 (Knezevic, 2008). We used Statins as the reference

group as it was the most prescribed medication in our study cohort.

To understand whether significant heterogeneity exists within each medication class, we performed further analysis to compare individual drug's with the hazard risk of the clinical onset of AD. The individual medications included in this study were Losartan (ARB), Valsartan (ARB), Lisinopril (ACEI), Atenolol (Beta Blocker), Carvedilol (Beta Blocker), Metoprolol (Beta Blocker), Labetalol (Beta Blocker), Propranolol (Beta Blocker), Metformin, Atorvastatin (Statin), Pravastatin (Statin), and Rosuvastatin (Statin). The analysis was conducted among patients who took only one of the above individual medications during the study period using the Cox proportional hazard models with and without PSW. Simvastatin was used as the reference group since it was the most prescribed medication in our study population and comparable with a number of comorbidities and clinical characteristics (Figure 2).

We also applied a permutation importance measure via a random forest approach to evaluate the relative importance of all investigated therapies in predicting the clinical onset of AD and identifying which predictors have a stronger association with the response (DuBrava et al., 2017; Phung et al., 2022; Loef et al., 2022). The selection of random forest over other frequently employed machine learning methods like neural networks and support vector machines stems from its dual advantages of predictive capability and interoperability. Demographic characteristics (age, race, sex), comorbidities, and prescription information for mono-and combined therapies of interest were included as exposures in the random forest model. We chose the permutation importance over the Gini importance in this study, as the permutation importance is considered more robust and less biased when dealing with categorical variables (Altmann et al., 2010). The area under the receiver operating characteristics curve (AUC) was reported to assess the accuracy of the algorithm.

Cox proportional hazard regression

Survival analysis is a set of statistical methods for analyzing the survival time of a particular population under study, commonly used to examine prognostic factors for mortality or occurrence of a disease and to study the outcome of treatment in the medical research (Agüero-Torres et al., 1998; Taktak and Fisher, 2006). Survival time or failure time is defined as the follow-up time from a defined starting point to the occurrence of a given event. The Kaplan–Meier methods, log-rank test, and Cox's proportional hazards model are frequently used survival analysis models, where two functions that are dependent on time are of particular interest: the survival function and the hazard function (Bewick et al., 2004).

The survival function S(t) represents the probability of surviving at least to time t, i.e., $S(t) = P(T \leq t)$. The hazard function h(t) is the conditional probability of the event of interest occurring in the next instant, given survival to time t, i.e., $h(t) = (d[lnS(t)])/dt$. The Kaplan–Meier method can be used to estimate the survival function without the assumption of an underlying probability distribution but cannot accommodate covariates (Gallin and Ognibene, 2012). The log-rank test, a non-parametric test, can be used to compare the equality of survival functions for two or more groups. The Cox proportional hazards model provides a framework for making inferences about covariates. Cox proportional hazards model does not apply assumption on the probability distribution of the hazard, while it assumes the hazard ratio among different groups holds constant over time.

Propensity score weighting

The propensity score analysis was introduced to address selection bias where random assignment between exposure and control groups is not feasible (Olmos and Govindasamy, 2015). Four commonly used propensity score methods are propensity score matching, stratification on the propensity score, propensity score weighting (or inverse probability of treat-

ment weighting using the propensity score), and covariate adjustment using the propensity score (Austin, 2011).

Some approaches have been proven to be preferred under different contexts (Elze et al., 2017). Depending on different settings, certain methods may eliminate a greater proportion of the systematic differences. The matching method was implemented by forming a matched untreated sample who shares a similar value of the propensity score to the treated subjects. The unmatched proportion will be eliminated from the estimation of the treatment effect. The weighting method that uses propensity score to adjust weights for individual observations and creates a synthetic sample based on all observations could make better use of the data (Olmos and Govindasamy, 2015).

Generalized boosted modeling

The essential part of the propensity score analysis is to obtain the propensity score. The propensity score represents the probability of a subject being treated. Transitionally, logistic regression was used to estimate the likelihood of receiving treatment. With the development in the field of machine learning, various machine learning techniques, such as tree-based methods and neural networks, had been introduced to estimate the propensity score as alternative options to logistic regression. In addition, leveraging of ensemble methods, like bagging and boosting algorithms, were claimed to yield more stable results and remove greater confounding effects (McCaffrey et al., 2004, 2013; Lee et al., 2010; Austin, 2012). Among them, generalized boosted modeling (GBM) or generalized boosted regression tree was the most commonly applied machine learning algorithm in propensity score analysis.

Random Forest

Random forest is a robust tree-based machine learning algorithm utilizing an ensemble learning method that has been widely used in bioinformatics with applications on genomic data analysis and health outcomes related prediction and classification (Chen and Ishwaran,

2012; Goldstein et al., 2010; Cafri et al., 2018; Khalilia et al., 2011). The algorithms can address two types of problems: 1) to perform prediction for classification and regression tasks; 2) to assess and rank variables in regard to their ability to predict the outcome (Boulesteix et al., 2012). The latter is done by ranking the variable importance scores, one of the primary outcomes of the random forest model, which reflects the relative importance of the variables in the prediction performance.

The variable importance ranking feature of the random forest procedure allows investigators to identify which predictors have a stronger association with the response. Recent studies have introduced the importance measure from a random forest model as an approach to assess the relative associations of risk factors and outcome diseases (DuBrava et al., 2017; Phung et al., 2022; Loef et al., 2022). The variable importance scores in the random forest were generally determined by two types of importance measures, the Gini importance and the permutation importance. The former was measured by Mean Decrease in Gini, which measures how each variable contributes to the homogeneity of the nodes and leaves in the random forest (Han et al., 2016). The latter was measured by the Mean Decrease in Accuracy, which captures the extent of model loss in out-of-bag accuracy by random permutation of the predictor of interest (Strobl et al., 2007). The higher the value of the mean decrease in Gini or mean decrease in accuracy, the higher the importance of the variable in predicting the outcomes.

2.3 Results

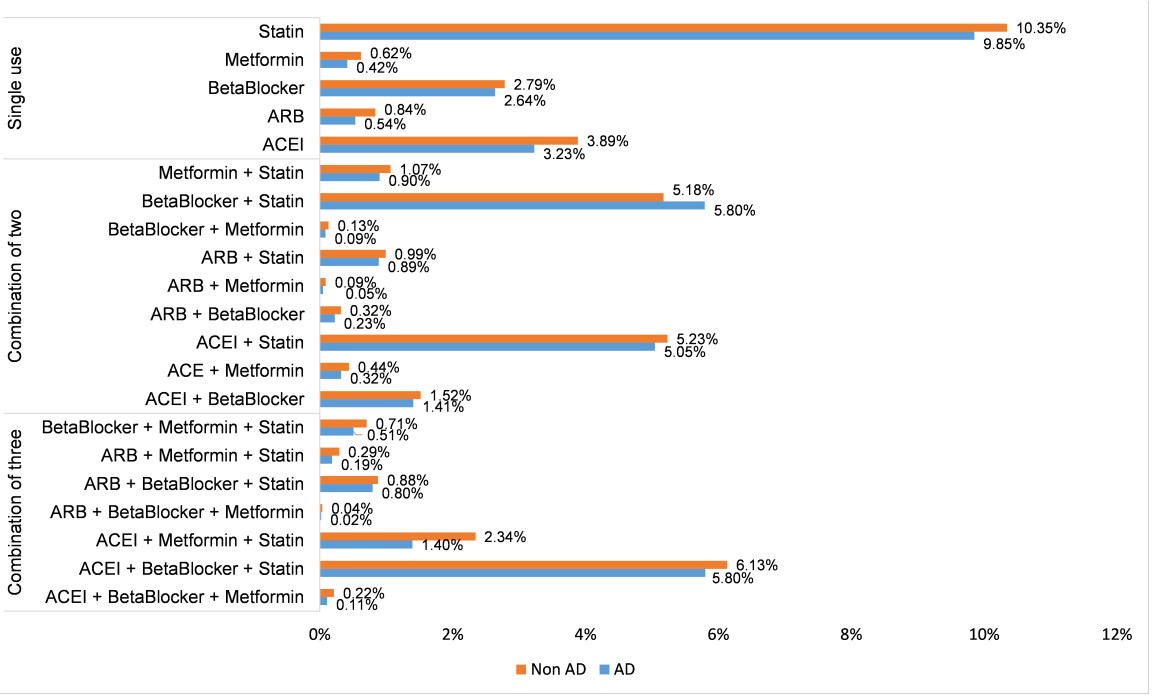
2.3.1 Demographic, clinical characteristics, and the medication use of the patients

Our study included 13,611 AD patients and 108,740 non-AD subjects in the VA VINCI database. The average age for non-AD patients (75.8 ± 6.8 yrs) was slightly lower than

AD patients (82.7 ± 5.1 yrs) (Table 2.1). The majority (AD group 98.19%, non-AD group 97.92%) of the study population is male (Table 2.1). AD patients appear to have a higher proportion of Hispanics (AD group 5.54%, non-AD group 3.57%)(Table 2.1).

The prevalence of the diseases among the study population at baseline, i.e. 65 years old, varies, and most subjects have hypertension, hyperlipidemia, and/or diabetes (Table 2.1). Overall, the proportions of different medications indicated were fairly comparable between the AD and non-AD groups, with the highest from the group using Statins alone (AD group 9.85% vs non-AD group 10.35%), followed by the group using ACEI+ Beta Blocker +Statin (AD group 5.80% vs non-AD group 6.13%), and the group using Beta Blocker +Statin (AD group 5.80% vs non-AD group 5.19%) (Fig 2.2).

Figure 2.2: Medication usage among AD patients and control subjects



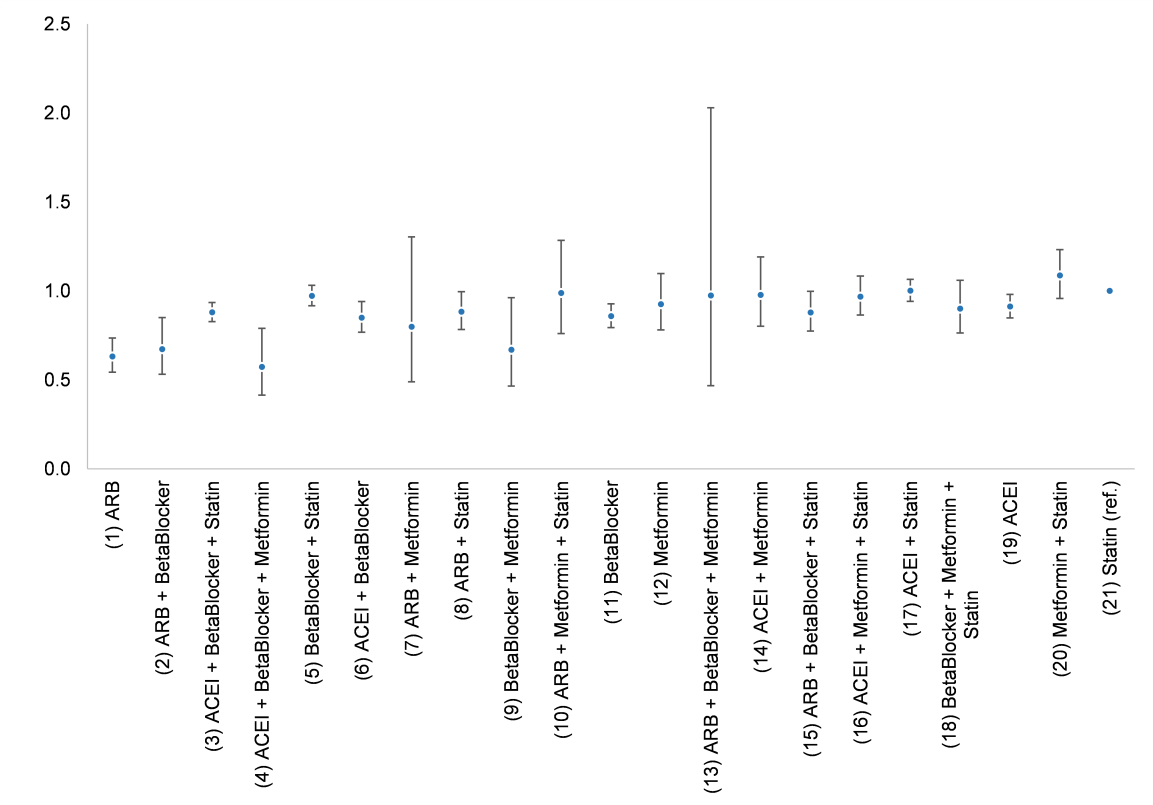
The graph reflects the distribution of the target medications for AD vs. non-AD group and the percentages for each medication group.

2.3.2 The use of ARB was associated with the lowest risk of AD onset among single medication users

For patients prescribed a single medication class the use of ARB (HR = 0.64, (0.55, 0.74)), Beta Blocker (HR = 0.86, (0.80, 0.92)), or ACEI (HR = 0.91, (0.85, 0.98)) was significantly associated with a reduced risk of AD onset compared to those prescribed with the Statin after adjustments for patients' demographic and comorbidity characteristics (Table 2.2). Patients prescribed ARBs demonstrated the strongest comparative beneficial effect with the lowest HR with PSW and the highest ranking of importance with random forest (Table 2.2), Fig 2.3). Patients prescribed Metformin (p-value = 0.164) did not reveal a statistically significant difference in AD onset risk compared with those prescribed Statins.

Compared to the singular use of ARB, the concomitant use of ARB with other medications did not further lower the risk of AD onset. The concomitant use of ARB + Beta Blocker (HR = 0.67, (0.54, 0.84)) and the singular use of ARB (HR = 0.64, (0.55, 0.74)) had comparable effectiveness, and both are with significantly reduced risk compared with the reference group (Statin). The concomitant use of ARB + Statin (HR = 0.88, (0.78, 0.99)) and ARB + Metformin + Statin (HR = 1.01, (0.79, 1.29)) did not appear to have a significantly more positive effect on AD onset than the singular use of ARB (Table 2.2), Fig 2.3). The combination of ARB with Metformin had no significant difference from the reference group.

Figure 2.3: Hazard ratios of the development of AD among combined medication users with importance ranking.



Statin was set as the reference group for the comparison of combined medications. The importance of combined therapies in predicting AD onset was measured by the mean decrease in accuracy (from the largest to the smallest). A higher mean decrease in accuracy is indicative of a more important variable, and the combinations are ordered from top to bottom as most to least important in predicting the development of AD.

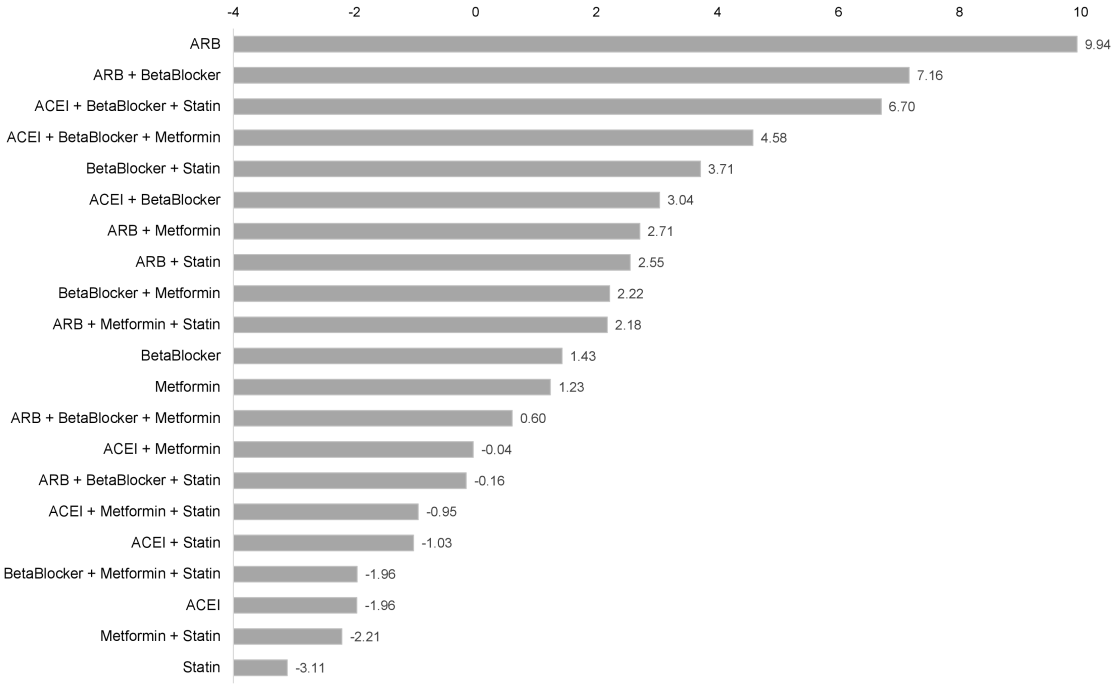
2.3.3 Metformin enhanced the effect of the ACEI + Beta Blocker

We found that the concomitant use of ACEI + Beta Blocker + Metformin (ABM) was associated with a lower risk of AD onset than ACEI, Betablocker or ACEI + Beta Blocker (p=0.0495) alone. This combined therapy ABM (HR = 0.56, 95%CI (0.41, 0.77)) appeared to have lower risk than the singular use of ACEI (HR = 0.91, (0.85, 0.98)), Beta Blocker (HR = 0.86, 95%CI(0.80, 0.92)), and ACEI + Beta Blocker (HR=0.85, 95%CI (0.77, 0.94)) (Table 2.2), Fig 2.3).

The result from the random forest analysis was consistent with the outcomes generated by

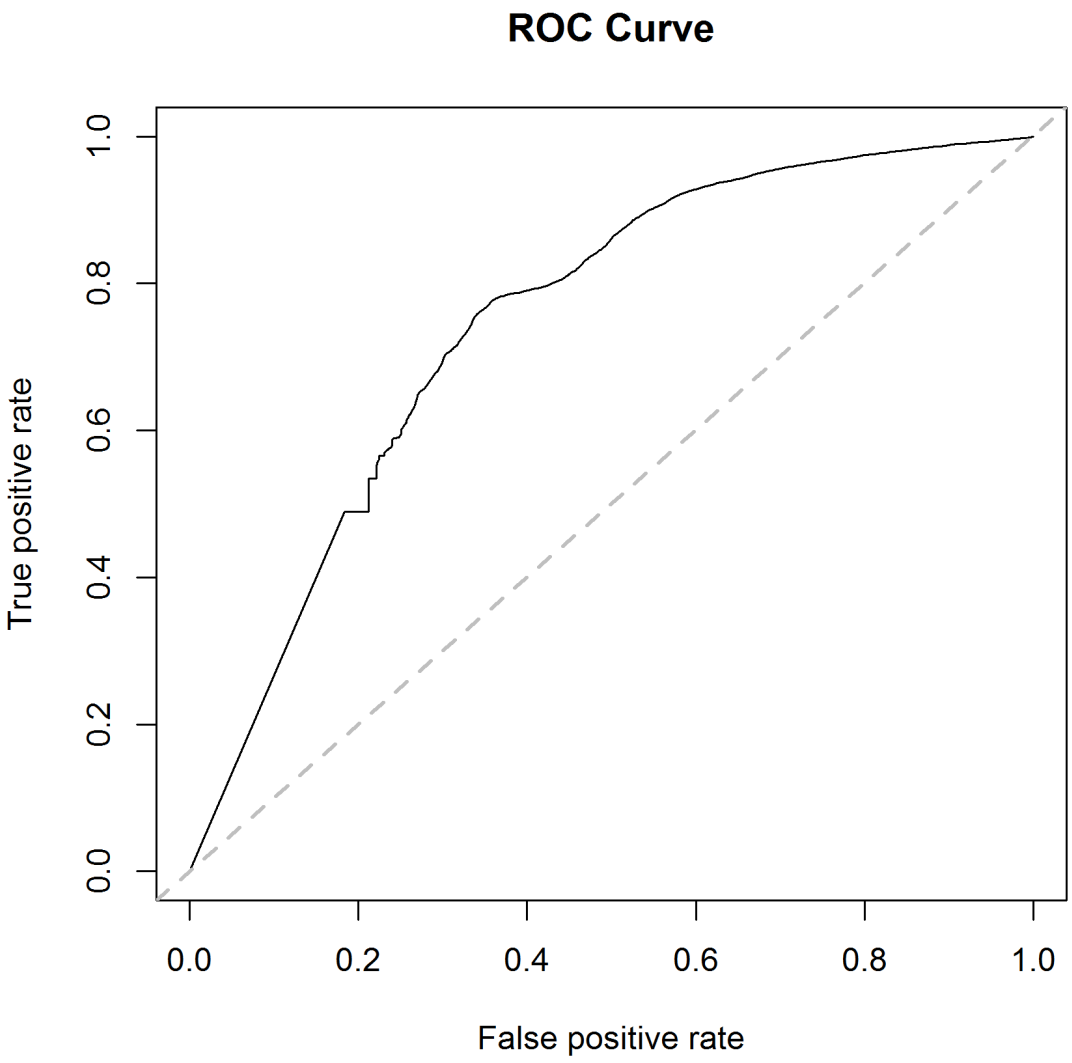
the Cox regression analysis, as the estimated mean of the HR generally increases as the importance ranking increases (Fig 2.3). In addition, the reported therapies that showed significant benefits in lowering the risk of AD onset had a higher importance ranking (from the random forest model) than their comparison therapies. There is no important difference between random forest and Cox regression analyses (Table 2.2, Fig 2.3), and Fig 2.4). The area under the receiver operating characteristics (ROC) curve (AUC) from the random forest model (Fig 2.5) was 0.75, highlighting the current model properly predicting the occurrence of AD (Naghibi et al., 2017).

Figure 2.4: Variable importance ranking of medication combinations from the Random Forest model



The importance was measured by the mean decrease in accuracy (from the largest to the smallest). A higher mean decrease in accuracy is indicative of a more important variable, and the combinations are ordered from top to bottom as most to least important in predicting the development of AD.

Figure 2.5: Receiver operating characteristic (ROC) curves of the random forest model that predicts the development of AD



2.3.4 Heterogeneity in efficacy among different medications from the same drug class on the risk of AD onset

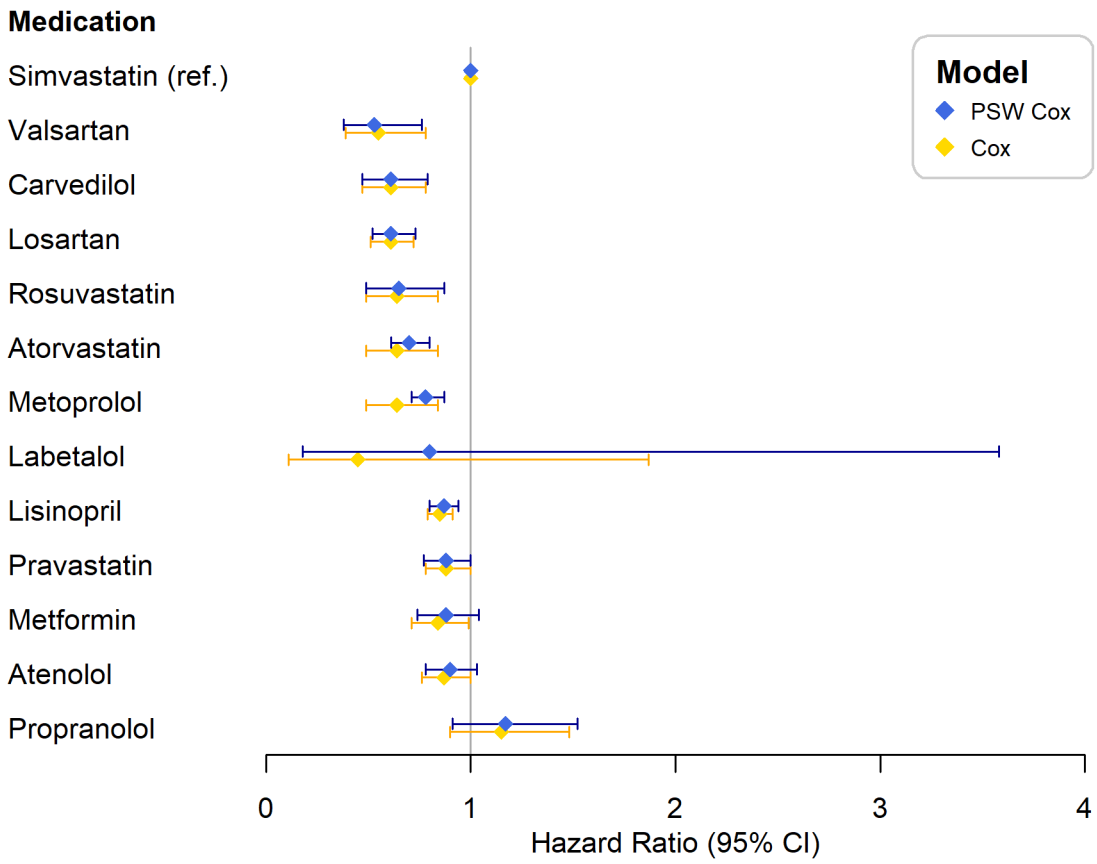
A comparison of HR of AD onset among patients prescribed single medications revealed that there was heterogeneity among different drugs within the same medication classes (Table 2.3). No significant difference at the 95% CI of HRs was observed within the class of

ARB (between Losartan and Valsartan) (Table 2.3, Fig 2.6). Both ARBs (Valsartan: HR = 0.55, (0.39, 0.78) and (Losartan: HR = 0.61, (0.51, 0.72)) outperformed the use of ACEI (Lisinopril: HR =, 0.85, (0.79, 0.91)), using Simvastatin users as a reference (Table 2.3, Fig 2.6).

However, differences among medications in the same class were observed for Statins and Beta Blockers. Compared to the use of Simvastatin, the use of Rosuvastatin (HR = 0.64, (0.49, 0.84)), Atorvastatin (HR = 0.64, (0.49, 0.84)) or Pravastatin (HR = 0.88, (0.78, 1.00)) demonstrated significantly reduced risks of AD onset (Table 2.3, Fig 2.6). As for Beta Blocker, Carvedilol (HR = 0.61, (0.47, 0.78)) and Metoprolol (HR = 0.64, (0.49, 0.84)) displayed lower HRs compared to Propranolol (HR = 1.15, (0.90, 1.48)) (Table 2.3, Fig 2.6).

Patients prescribed Metformin did not reveal a significant difference in the risk of AD onset when compared with any medication under the class of Statin (Table 2.3), which was consistent with the result from class-level analysis (Table 2.2).

Figure 2.6: Hazard ratios (HR) of the development of AD among singular users at individual medication level.



Simvastatin was used as a reference drug (hazard ratio = 1). All other medications discussed in this study illustrate variable hazard ratios predicting the onset of AD.

2.4 Discussion and Conclusion

Aging is the primary risk factor contributing to dementia in the elderly, and successful aging, free from dementia, can be defined as a prolongation of the "pre-symptomatic" period of neurodegenerative diseases like AD with a proper cognitive reserve and brain maintenance (Stern et al., 2020). The concomitant use of multiple medications was very common for elderly patients with one or multiple comorbidities. Over 70% of patients with hypertension require at least two antihypertensive agents when blood pressure is not adequately

controlled by monotherapy, particularly if subjects have comorbid conditions (Smith et al., 2020; Frank, 2008). Concomitant use of multiple medications is common for many hypertension patients with comorbid conditions.

This study uses the dataset from the largest single healthcare system from the Veterans Health Administration to understand the association of mixed use of commonly prescribed medications with the risk of AD onset. We explored the comparative effectiveness of the concomitant use of multiple therapies for prolongation of the pre-symptomatic survival time to AD onset, with a general tactic of repurposing existing FDA-approved drugs for other indications as an alternative approach for AD treatment. The risks (hazard ratios) of AD onset were compared among patients with one, two, or three FDA-approved medications which are widely prescribed to AD patients. Among the investigated medication classes (i.e., ARBs, ACEI, Beta Blocker, Metformin, and Statins), the greatest protective effect was associated with ARB use, followed by Beta Blocker, and ACEI, among patients who took only one of the investigational medication classes. Metformin class seemed to perform slightly better than the class of Statin medications, while the difference was not significant. There have been no other published works that have examined the use of three combination drug classes in large databases focusing on their associations with AD onset.

ARB appeared to be the most effective monotherapy with a lower risk for the onset of AD among the five investigated medication classes. A recent meta-analysis exhibited that ARB use was associated with a reduced risk of incident AD both in a randomized controlled trial and also in observational studies (Oscanoa et al., 2021). Analysis of post-mortem brain tissue from AD or non-AD subjects suggests that ARB use was associated with fewer amyloid plaques compared to treatments with other classes of antihypertensive medications or with no medications (Hajjar et al., 2012). Our results corroborate our previous hypothesis of the beneficial effect of ARB use on patients with dementia (Li et al., 2010).

When comparing two first-line therapies for the treatment of hypertension, patients pre-

scribed medications in the ARB class were associated with a lower risk of AD onset compared with those patients who were prescribed ACEI. Patients prescribed ARB medications also had a lower risk of AD onset than patients prescribed with other anti-hypertensive agents, Beta Blockers. Despite being markedly superior to Simvastatin, the combined therapy of ARBs + Beta Blockers did not show a significant additive effect on reducing the risk of AD onset when compared to the monotherapy of either ARBs or Beta Blockers.

In addition, we found that adding metformin to the combination of ACEI + Beta blocker improved the effectiveness of the medication in lowering the risk of AD, compared with monotherapies ACEI or Beta blocker or combination of ACEI + Beta blocker. ACEI (Lisinopril), the first-line anti-hypertensive agent, and Metformin, a favored oral management of diabetes, are frequently prescribed together. Except for the major indications, these two medications have renoprotective and cardioprotective properties, respectively, and the concomitant use of Lisinopril and Metformin increased the blood glucose lowering effects of Metformin (Amorha et al., 2013), while significantly decreasing blood pressure variability and mean blood pressure (Hakim et al., 2021). Evidence supports the benefits of the combined therapy of ACEI + Beta Blocker in patients with a broad spectrum of cardiovascular diseases (Strauss et al., 2021). As such, it is reasonable to postulate that the combination therapy of ACEI + Beta Blocker + Metformin may achieve improved management of comorbid conditions and provide additional benefits.

Our result from this study echoes the concern of reversible memory impairment among patients with Statin therapy, which makes it unadvisable to use Statins for AD patients (King et al., 2003; Wagstaff et al., 2003; Evans and Golomb, 2009). The FDA's post-marketing safety surveillance system revealed several case reports of Statin-associated memory loss and improvement after discontinuation of the Statin and issued a warning regarding the potential adverse effects of statins on cognition in 2012. Multiple reviews and meta-analyses did not indicate substantial evidence to support that Statins cause cognitive impairment to a

significant degree and fail to establish the causal relationship (Samaras et al., 2016; Bitzur, 2016; Ott et al., 2015; Richardson et al., 2013). The current understanding of Statins' effect on cognitive function is limited by a lack of mechanism-based studies. We found that there was some heterogeneity existing within a given medication class. The HR of AD onset varies widely among Statins and Beta Blockers. Our results suggest Simvastatin appeared to be the least protective medication among Statins. Patients prescribed Rosuvastatin, Atorvastatin, or Pravastatin had lower HRs of AD onset than those prescribed Simvastatin. The risks of AD onset in patients prescribed Rosuvastatin, Atorvastatin, and Pravastatin were approximately 35%, 30%, and 12% lower compared to those prescribed Simvastatin, respectively. This result was consistent with an early report that Pravastatin, but not Simvastatin, was associated with a reduced risk of AD onset (Wolozin et al., 2000). Our results support the previous notion that individual Statins may contribute in unique ways to the central nervous system (McFarland et al., 2014). The mechanisms by which the cholesterol-lowering effects of Statins contribute to the pathogenic process of AD remain unclear. It is unclear whether the possible effects of Statin use mainly work through brain cholesterol metabolism, peripheral cholesterol metabolism, or both. A clear understanding of the relationship between brain cholesterol homeostasis and AD is yet to be fully elucidated.

The comparative effectiveness against AD among Beta Blockers trails behind the development of newer Beta Blockers. In this study, Carvedilol and Metoprolol were associated with reduced risk of AD compared to Propranolol.

Our study is subject to several limitations. First, the identification of AD clinical diagnoses was based on the ICD coding system, which is a widely accepted method for identifying medical conditions in large-scale administrative health data. Although comorbidities are often under-reported in administrative data, the validity of using ICD codes to study neurologic conditions is generally consistent with that of patient chart data for the recording of co-

morbidities (Germaine-Smith et al., 2012; Quan et al., 2002; Taylor Jr et al., 2002). Previous analyses have indicated a high level of specificity in identifying AD and dementia cases using ICD codes across several studies (over 84%) (Germaine-Smith et al., 2012). Sensitivity was found to be higher when both inpatient and outpatient records were taken into account based on ICD code (Germaine-Smith et al., 2012), which is a similar approach adopted in our study. The underestimation of Alzheimer's disease and other dementia prevalence through ICD coding in the VA healthcare system may be attributed to the excessive use of non-specific dementia codes (Butler et al., 2012). The change of coding systems from ICD 9 to ICD 10 during the study period may have had a limited impact on the result since the validity of ICD 10 was generally similar to that of ICD 9 (Quan et al., 2008).

Second, our study population consists of a large group of Veterans who use the VA healthcare system and are largely male, exhibiting more physical and mental health conditions than would be found in a general community-wide population. In general, our cohort of non-AD subjects had a slightly higher prevalence of several comorbidity conditions at a baseline of 65 years or older than the cohort of AD patients. Third, residual confounding factors and unmeasured variables may exist even though we have incorporated the adjustment for potential known confounders, which is common in observational studies.

Fourth, we do not know the potential mechanisms of action for the combined therapies, other than their effects on their known indications, that made some of them superior to the others. The candidate combination therapy has yet to be fully elucidated for its impact on AD progression and alteration of AD-related biomarkers. Fifth, the combined use of medications should be carefully examined to identify the nature of any potential beneficial effects and minimize adverse drug interactions. For example, strong evidence supports the concept that a combined therapy of ACEI and ARB could significantly worsen renal failure in patients with chronic kidney disease (Onuigbo, 2011) 57. Nevertheless, concurrent use of two or more medications with different underlying mechanisms could increase the success

rate of drug repositioning because of the possible synergistic effects, as well as the reduction or delay of the development of drug resistance (Sun et al., 2016).

While we do not believe our findings justify a change in clinical practice, these results warrant further investigation using additional cohorts to determine if the future findings are comparable. Future efforts to validate these combination drugs in clinical settings when new AD therapy is offered will provide a reliable prediction about the likelihood of conversion from the pre-symptomatic stage to the clinical stage of AD for subjects who have been taking combined medication therapies.

Table 2.1: Demographic and co-morbidity distribution of study subjects

		non-AD (108,740)	AD (13,611)
		Mean(SD)	Mean(SD)
Age		75.80 (6.82)	82.72 (5.08)
		Count (%)	Count (%)
Sex	Male	106,482 (97.92%)	13,365 (98.19%)
	Female	2,258 (2.08%)	246 (1.81%)
Race	White	96,921 (89.13%)	12,226 (89.82%)
	American Indian or Alaska	729 (0.67%)	67 (0.49%)
	Asian	555 (0.51%)	43 (0.32%)
	Black or African American	8,995 (8.27%)	1,080 (7.93%)
	Native Hawaiian or Other Native	977 (0.9%)	120 (0.88%)
	Unknown	563 (0.52%)	75 (0.55%)
Ethnicity	Hispanic or Latino	3,884 (3.57%)	754 (5.54%)
	Not Hispanic or Latino	102,904 (94.63%)	12,596 (92.54%)
	Unknown	1,952 (1.8%)	261 (1.92%)
Hypertension		47,289 (43.49%)	2,490 (18.29%)
Hyperlipidemia		47,148 (43.36%)	2,474 (18.18%)
Depression		18,414 (16.93%)	999 (7.34%)
Tobacco Use		18,526 (17.04%)	582 (4.28%)
Obesity		20,035 (18.42%)	728 (5.35%)
Lung disease		16,754 (15.41%)	774 (5.69%)
Coronary artery disease		16,607 (15.27%)	1099 (8.07%)
Diabetes		15,099 (13.89%)	741 (5.44%)
Anxiety		10,863 (9.99%)	519 (3.81%)
Post-traumatic stress disorder		10,957 (10.08%)	441 (3.24%)
Alcohol		9,534 (8.77%)	305 (2.24%)
Cardiac dysrhythmia		8,370 (7.7%)	392 (2.88%)
Cancer		7,679 (7.06%)	286 (2.1%)
Peripheral arterial disease		7,050 (6.48%)	326 (2.4%)
Sleep disorder		5,963 (5.48%)	211 (1.55%)
Hypothyroidism		5,294 (4.87%)	254 (1.87%)
Congestive heart failure		4,330 (3.98%)	191 (1.4%)
Renal failure		4,003 (3.68%)	130 (0.96%)
Substance use disorders		3,176 (2.92%)	96 (0.71%)
Stroke		3,668 (3.37%)	200 (1.47%)
Bipolar		3,357 (3.09%)	185 (1.36%)
Liver disease		2,032 (1.87%)	42 (0.31%)
Schizophrenia		1,764 (1.62%)	122 (0.9%)
Dementia		1,129 (1.04%)	165 (1.21%)
Traumatic brain injury		1,084 (1%)	58 (0.43%)

Table 2.2: Characteristics of study subjects using target medications

Importance Ranking	Therapy	Propensity Score Weighted Cox			Cox		
(Random Forest)		HR	95% CI	P-value	HR	95% CI	P-value
1	ARB	0.63	(0.54,0.74)	<0.001	0.64	(0.55,0.74)	<0.001
2	ARB + Beta Blocker	0.67	(0.53,0.85)	0.001	0.67	(0.54,0.84)	0.001
3	ACEI + Beta Blocker + Statin	0.88	(0.83,0.94)	<0.001	0.89	(0.84,0.94)	<0.001
4	ACEI + Beta Blocker + Metformin	0.57	(0.42,0.79)	0.001	0.56	(0.41,0.77)	<0.001
5	Beta Blocker + Statin	0.97	(0.92,1.03)	0.354	0.97	(0.92,1.03)	0.328
6	ACEI + Beta Blocker	0.85	(0.77,0.94)	0.002	0.85	(0.77,0.94)	0.001
7	ARB + Metformin	0.8	(0.49,1.30)	0.369	0.76	(0.47,1.23)	0.269
8	ARB + Statin	0.88	(0.78,1.00)	0.042	0.88	(0.78,0.99)	0.029
9	Beta Blocker + Metformin	0.67	(0.47,0.96)	0.03	0.7	(0.49,1.00)	0.051
10	ARB + Metformin + Statin	0.99	(0.76,1.28)	0.931	1.01	(0.79,1.29)	0.949
11	Beta Blocker	0.86	(0.79,0.93)	0	0.86	(0.80,0.92)	<0.001
12	Metformin	0.93	(0.78,1.10)	0.375	0.89	(0.75,1.05)	0.164
13	ARB + Beta Blocker + Metformin	0.97	(0.47,2.03)	0.945	0.92	(0.46,1.85)	0.824
14	ACEI + Metformin	0.98	(0.80,1.19)	0.82	0.95	(0.78,1.15)	0.569
15	ARB + Beta Blocker + Statin	0.88	(0.77,1.00)	0.047	0.87	(0.77,0.99)	0.029
16	ACEI + Metformin + Statin	0.97	(0.86,1.08)	0.576	0.94	(0.85,1.04)	0.216
17	ACEI + Statin	1	(0.94,1.06)	0.963	1	(0.95,1.07)	0.875
18	Beta Blocker + Metformin + Statin	0.9	(0.76,1.06)	0.208	0.91	(0.78,1.06)	0.229
19	ACEI	0.91	(0.85,0.98)	0.013	0.91	(0.85,0.98)	0.008
20	Metformin + Statin	1.09	(0.96,1.23)	0.196	1.11	(0.98,1.24)	0.097
21	Statin (ref.)						

Table 2.3: Association of individual medications with the development of AD (Simvastatin as reference).

	Propensity Score Weighted Cox			Cox		
	HR	95% CI	P-value	HR	95% CI	P-value
Valsartan	0.53	(0.38,0.76)	<0.001	0.55	(0.39,0.78)	0.001
Carvedilol	0.61	(0.47,0.79)	<0.001	0.61	(0.47,0.78)	<0.001
Losartan	0.61	(0.51,0.73)	<0.001	0.61	(0.51,0.72)	<0.001
Rosuvastatin	0.65	(0.49,0.87)	0.003	0.64	(0.49,0.84)	0.001
Atorvastatin	0.7	(0.61,0.80)	<0.001	0.64	(0.49,0.84)	0.001
Metoprolol	0.78	(0.71,0.87)	<0.001	0.64	(0.49,0.84)	0.001
Labetalol	0.8	(0.18,3.58)	0.766	0.45	(0.11,1.87)	0.271
Lisinopril	0.87	(0.80,0.94)	<0.001	0.85	(0.79,0.91)	<0.001
Pravastatin	0.88	(0.77,1.00)	0.048	0.88	(0.78,1.00)	0.059
Metformin	0.88	(0.74,1.04)	0.14	0.84	(0.71,0.99)	0.04
Atenolol	0.9	(0.78,1.03)	0.12	0.87	(0.76,1.00)	0.044
Propranolol	1.17	(0.91,1.52)	0.225	1.15	(0.90,1.48)	0.269

Chapter 3

Clinical transition to Alzheimer's disease in individuals with mild cognitive impairment who progressed to Alzheimer's disease

3.1 Introduction

Mild cognitive impairment (MCI) has become particularly important as it has been defined as the transitional state between normal aging and early Alzheimer's disease (AD) (Petersen, 2000). MCI due to AD was considered a clinically critical phase that provides an opportunity for early detection and intervention before significant neurodegeneration is widespread across different brain regions.

MCI is defined as an impaired cognitive state which does not meet the criteria for the diagnosis of dementia (Petersen, 2004; Nesteruk et al., 2015). Although the likelihood of transition from MCI to any form of dementia has been suggested to be 3 to 5 times higher than those transitions from normal cognition, not all MCI result from pathologic changes of AD (Campbell et al., 2013; Ganguli et al., 2019). Other conditions, such as cardiovascular diseases, hypertension, diabetes, depression, anxiety, hypercholesterolemia, and

smoking (Reitz et al., 2007; Ma, 2020; Vintimilla et al., 2020; Dufouil et al., 2005; Chen et al., 2021), have been found to contribute to cognitive dysfunction and lead to MCI. While few subjects with MCI recover and reverse to near-normal conditions, and many remain stable with MCI (Pandya et al., 2016). In clinical practice, to determine whether someone with MCI may convert to AD, a clinician must rule out other causes that account for the cognitive changes, such as depression and related medications that may affect the conversion from MCI to AD (Bartels et al., 2018). As such, it is important to understand how MCI transits to AD. The transition probability can be used for the estimation of cost and healthcare utilization for MCI/AD patients. Previous works presented a large difference in the transition probability from MCI to AD, ranging from 1% to 34% per year (Potashman et al., 2021; Petersen et al., 1999; Bruscoli and Lovestone, 2004; Dawe et al., 1992; Ward et al., 2013). The wide range of differences arises from the limited sample size, diverse interpretations of MCI used in the analysis, and the analytical approach employed (Bruscoli and Lovestone, 2004; Dawe et al., 1992). The sample sizes of many studies were less than 100 subjects. Other factors reported to affect the estimated conversion rate included the recruitment source, follow-up years, whether account for loss to follow-up, demographic/genetic/biomarker characteristics, and the lifestyles of the patients (Ward et al., 2013; Varatharajah et al., 2019; Davatzikos et al., 2011). In addition, limited studies have attempted to estimate transitions across the full disease continuum (Potashman et al., 2021).

The current study used an advanced approach, the Multistate Markov Cox Regression model, to estimate the transition probabilities between stages of Alzheimer's disease (MCI, AD, and Death).

The Multi-state Markov model is an emerging approach that estimates the transition probability among multiple states simultaneously (Meira-Machado et al., 2009). Recently, this apporach has been applied to investigating the progression of Alzheimer's disease. Zhang et al. (2019) has applied a Multi-state Markov model to investigate the significance of de-

mographic and MRI regional volumetric risk factors in predicting transitions between normal conditions, MCI, and AD using Alzheimer's Disease Neuroimaging Initiative (ADNI) data. Another study used a Multi-state Markov model to analyze the transitions from MCI to global impairment, then to AD in a community-based MCI cohort in China (Yu et al., 2013).

The current study emphasizes the transitions from MCI to AD to Death. Death was treated as the absorbing state and the competing risk of AD in the model. Besides, this study controlled and investigated the effect of medication usage of antihypertensive agents, lipid-lowering agents, medication for diabetes, and medication for Alzheimer's disease's symptoms, which were not included in the previous Multistate Markov studies.

Epidemiological studies have identified various modifiable comorbidity risk factors for the transition from MCI to dementia/AD. As such, it is important to know whether the use of FDA-approved medication for treating the known comorbidity risk factors of AD might contribute to delaying disease progression. Also to investigate the association of the use of medications for these comorbidity risk factors of AD with the risks of transitions of disease progression. The investigated medications for the modifiable risk factors of AD included antihypertensive agents, lipid-lowering agents, and medication for diabetes.

Acquiring knowledge about the broad temporal progression of the disease and the associated risk factors along its trajectory holds the utmost importance in advancing health outcomes, healthcare services, and policy within the aging population. This research endeavor assumes a pivotal role in guiding early detection strategies, optimizing treatment approaches, informing resource allocation decisions, shaping health policies, and empowering individuals affected by the disease.

3.2 Method

3.2.1 Study Design

This is a cohort-based case-control study in a multiple endpoint setting using data from National Alzheimer's Coordinating Center (NACC) over the period between September 2005 and May 2021. The investigated cohort is individuals with clinically diagnosed MCI. The analysis includes three stages throughout the AD progression, that is, state MCI, state AD, and state death. State MCI is the initial state. State AD is the first endpoint. And state death is the second endpoint and the absorbing state.

The aims of this study are:
RQ1: 1. Identifying the transition probabilities along the disease progression of AD (MCI, AD, death) and total length of stay at each stage.

RQ2: Determining the medications (for the modifiable risk factors of AD) that affect transition time from MCI to AD, MCI to death, and AD to death.

3.2.2 Data Source and Study Population

We used data from the National Alzheimer's Coordinating Center (NACC), which adopted a prospective, standardized, and longitudinal clinical evaluation of the subjects in the National Institute on Aging's ADRC Program. Data are collected by trained clinicians and clinic personnel from participants and their co-participants. All diagnoses are made by either a consensus team or a single physician who conducted the examination.

The population of this study is those who had been diagnosed with MCI and had at least two visits during a period between September 2005 and May 2021. We removed patients with massive missing information on comorbidities. The AD patients (patients who have/had been in the state of AD) were those who had no reversed clinical diagnoses of AD dur-

ing past visits. The reversed diagnosis of AD can be a result of a rule-out diagnosis or a misdiagnosis.

Therefore, those MCI patients who had reversed clinical diagnoses of AD were considered to be MCI patients without AD. The MCI patients were identified based on the presence of at least two MCI diagnoses, as considering a single MCI diagnosis alone could potentially lead to excluding relevant cases. Deceased patients (patients who were finally in the state of Death) are those whose death was reported to NACC. With all inclusion and exclusion criteria mentioned above, finally, we obtained 3,324 qualified MCI patients.

3.2.3 Study Variables

Outcome variables

The outcome variables are the times to transition from state to state. For example, the transition time from state MCI to state AD is defined as the time from the first MCI diagnosis to the first AD diagnosis.

Medications that May Impact Transition Times

The investigated medications included antihypertensive agents, lipid-lowering agents, medication for diabetes, and medication for Alzheimer's disease symptoms. The use of medication was considered as "current use" if the patient report the use of this medication within two weeks before the visit. The possible associations of the current use of investigated medications with all transitions were evaluated.

Covariates

Demographic characteristics, APOE genotype, and several known comorbidity risk factors were adjusted in the model. Demographic characteristics included age, gender, race, and ethnicity. The comorbidities included cardiovascular diseases (heart attack, conges-

tive heart failure, stroke, Transient ischemic attack), diabetes, hypertension, hypercholesterolemia, seizures, B12 deficiency, thyroid, and the substance use of alcohol. All comorbidities were assessed by the clinician, not self-report comorbidities. All comorbidities take values of either "recent present" or "no". A disease was "recent present" if it is active in the past year or still requires active management and is consistent with information obtained from the subject and co-participant interview.

3.2.4 Statistical Analysis

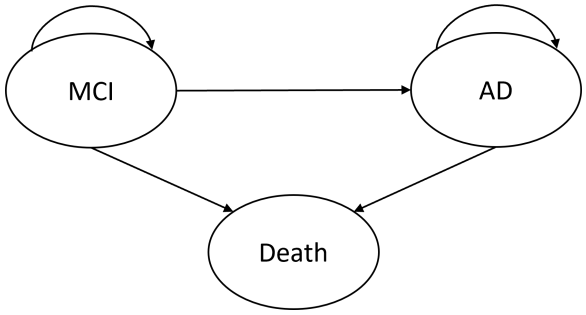
Descriptive statistics were used to present demographic characteristics, APOE genotype, and baseline comorbidities for the study cohort; counts and percentages were used for categorical variables, and means and standard deviations were used for continuous variables.

The Multi-state Markov model is a well-established approach that describes a stochastic process where more than one destination state exists, and it allows us to estimate the transition rates among multiple states simultaneously (Andersen and Keiding, 2002). An important advantage of this method is that it can be implemented to accommodate intermittent observations, which is very common for longitudinal studies (Cook and Lawless, 2018). Covariates can be fitted in the form of the Cox regression model (Andersen and Keiding, 2002; Le-Rademacher et al., 2018).

We postulated a three-state Markov Cox Regression model to capture the disease progression from MCI to AD to death (Fig 3.1). To be specific, we used Time-homogeneous Multistate Markov Cox regression models to 1) Estimate the transition probabilities for all transitions: MCI-MCI, MCI-AD, MCI-death, AD-AD, AD-death, as well as the total length of stay in each state; 2) Evaluate the hazard risk of the use of medication for the known comorbidity risk factors for all transitions. The model was controlled for possible confounding effects for demographic, genetic characteristics, and comorbidities. Transition intensity, the transition probabilities, the total length of stay at each state, and the hazard ratios (HR) of

investigated medication usage for each transition with 95% confidence intervals (CI) were reported.

Figure 3.1: Multi-state modeling diagram



Flow diagram of AD disease progression transitions.The three phases were MCI (mild cognitive impairment), AD (Alzheimer's' disease), and Death.

Multi-State Markov model

A multistate Markov model is a common model for describing the development of longitudinal failure data (Hougaard, 1999). It describes a stochastic process where more than one destination state exists and it allows to estimate the transition rates among multiple states (Meira-Machado et al., 2009; Therneau et al., 2020). It can be used to analyze the disease progression. States could be different stages of a disease. A change of state is called transition. A state structure defines states and which transitions from state to state are possible (Hougaard, 1999). One advantage of the multi-state Markov model is it can specify the state structure flexibly. Therefore it could easily deal with complex structures and include competing risks.

A transition of a multi-state model with n states can be characterized by a transition matrix

Q:

$$Q = \begin{pmatrix} q_{11} & q_{12} & \cdots & q_{1n} \\ q_{21} & q_{22} & \cdots & q_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ q_{n1} & q_{n2} & \cdots & q_{nn} \end{pmatrix} \tag{3.1}$$

, where each element q_{hj} in the matrix Q is the transition rate from state h to state j.

A multistate process is a stochastic process (X (t), t ∈ T) with finite state space S = {1, 2, 3, 4, 5, ...} where T = [0, τ], $\tau < \infty$ is the period of observation (Matsena Zingoni et al., 2019). A well-established method of estimating the transition rates between states is the one relying on the Markov processes in which the transition rates only depend on the current state (i.e., independent of the history of the process prior to entry to the destination state). For a continuous-time Markovian process, the transition rate (or instantaneous incidence rate, or transition intensity) $q_{hj}(t)$ of a patient from state X(t) = h at time t to state j at time t + Δ t is defined as:

$$q_{hj}(t) = \lim_{\Delta t \to 0} p_{hj} \frac{(t, t + \Delta t)}{\Delta t} \tag{3.2}$$

where $p_{hj}(t)$ is the transition probability from state h to j in a multi-state process.

The transition probabilities can be calculated from the transition rates (intensities) under the Markov assumption by solving Kolmogorov differential equation (Cox and Miller, 2017). The transition rate (intensity) measures the average number of events (transitions) per unit of time. The transition probability represents the conditional probability of entering state j at time t, given the system was in state i at time 0.

In a time-homogeneous Markov model where all transition intensities are assumed to be

constant over time. For a three-state illness-death model as we presented in (Fig 3.1), the transition rate matrix can be expressed as:

$$Q = \begin{pmatrix} -(q_{12} + q_{13}) & q_{12} & q_{13} \\ 0 & -q_{23} & q_{23} \\ 0 & 0 & 0 \end{pmatrix} \tag{3.3}$$

, whose rows sum to 0, the diagonal elements are the conversions from h to h as $q_{hh}(t) = -\sum_{h \neq j} q_{hj}(t)$ for all j $\in$ T.

The transition probability $p_{hj}(t)$ can be calculated by taking the matrix exponential of the scaled transition intensity matrix (Jackson, 2007). The transition probabilities at corresponding time t are:

$$p_{11}(t) = e^{-(q_{12}+q_{13})t} \tag{3.4}$$

$$p_{12}(t) = \frac{q_{12}}{q_{12} + q_{13} - q_{23}}(e^{-q_{23}} - e^{-(q_{12}+q_{13})t}) \tag{3.5}$$

$$p_{13}(t) = 1 - e^{-(q_{12}+q_{13})t} - \frac{q_{12}}{q_{12} + q_{13} - q_{23}}(e^{-q_{23}} - e^{-(q_{12}+q_{13})t}) \tag{3.6}$$

$$p_{21}(t) = 0 \tag{3.7}$$

$$p_{22}(t) = e^{-q_{23}t} \tag{3.8}$$

$$p_{23}(t) = 1 - e^{-q_{23}t} \tag{3.9}$$

$$p_{31}(t) = 0 \tag{3.10}$$

$$p_{32}(t) = 0 \tag{3.11}$$

$$p_{31}(t) = 1 \tag{3.12}$$

The maximum likelihood estimation can be used to infer these transition rates as a product of probabilities of transition between observed states, over all individuals. Suppose i indexes M individuals. For each individual i $\in$ M consist of a series of times $(t_{i,0}, t_{i,0}, \cdots, t_{i,n_i})$

and corresponding states ($(S_{i,0}, S_{i,0}, \cdots, S_{i,n_i})$). For a successive observed transition from states S_{t_j} to $S_{t_{j+1}}$ at time t_j to t_{j+1}, the likelihood of the transition probability for the ith individual, denoted as $L_{i,j}$, is the entry of the transition probability matrix p(t) at the S_{t_j}th row and S_{t_j+1}th column, evaluated at $t = t_{j+1} - t_j$:

$$L_{i,j} = p_{S_{(t_j)}S_{(t_{j+1})}}(t_{j+1} - t_j) \tag{3.13}$$

The likelihood L(Q) is the product of all $L_{i,j}$ over all individuals and all transitions:

$$L(Q) = \prod_{i=1}^{m} \prod_{r=0}^{n_{i-1}} L_{i,j} \tag{3.14}$$

In a special case where the exact transition times (not the observed transition times) are available for q_{ij}, the maximum likelihood estimator of the constant transition rate is the "occurrence/exposure rates" (Andersen and Perme, 2008):

$$\hat{q_{ij}} = \frac{N_{i,j}}{D_i} \tag{3.15}$$

, where $N_{i,j}$ is the total number of observed transitions from state i to state j and D_i is the total number of patient-days in state i.

3.3 Results

3.3.1 Study population: demographics, APOE genotype, comorbidities, and medication usage at baseline

3,324 MCI patients were included in the analysis. The average age at the initial visit of the study subjects was 73.1 ± 9.7 years. 50.2% of the study subjects were male, and 49.8% were female. The majority were white (80.6%) and non-Hispanic (91.2%). The most common

Table 3.1: Study subjects' demographics and APOE genotype profile

		Mean (SD)
Age at the initial visit		73.1 (9.7)
		Count (%)
Gender	Male	1667 (50.2%)
	Female	1657 (49.8%)
Race	White	2680 (80.6%)
	Black or African American	487 (14.7%)
	Asian	69 (2.1%)
	American Indian or Alaska	23 (0.7%)
	Other/Unknown	65 (2.0%)
Ethnicity	Not Hispanic or Latino	3031 (91.2%)
	Hispanic or Latino	282 (8.5%)
	Unknown	11 (0.3%)
APOE	e3, e3	1505 (45.3%)
	e3, e4	779 (23.4%)
	e3, e2	302 (9.1%)
	e4, e4	141 (4.2%)
	e4, e2	78 (2.3%)
	e2, e2	16 (0.5%)
	Unknown	503 (15.1%)

APOE genotype is e3, e3 (accounts for 45.3% of the study subjects), followed by e3, e4 (23.4%), e3, e2 (9.1%), e4, e4 (4.2%), e4, e2 (2.3%), and e2, e2 (0.5%) (Table 3.1).

Hypertension (53.3%) and hypercholesterolemia (52.6%) were the top comorbidity burdens for the study cohort, followed by diabetes (15.6%) and thyroid (15.3%) (Table 3.2). The prevalences for cardiovascular diseases, b12 deficiency, seizures, and substance abuse of alcohol were 7.0%, 3.3%, 1.3%, and 0.8% respectively (Table 3.2).

59.5% of study subjects had current use of any type of antihypertensive or blood pressure medication at the beginning of the study (Table 3.3). The current use of lipid-lowering medication, FDA-approved medication for Alzheimer's disease symptoms, and diabetes medication at the baseline were 46.1%, 16.8%, and 12.6% (Table 3.3).

Table 3.2: Baseline comorbidity burden of the study subjects

	Yes	No
Hypertension	2772 (53.3%)	1552 (46.7%)
Hypercholesterolemia	1749 (52.6%)	1575 (47.4%)
Thyroid	507 (15.3%)	2817 (84.7%)
Diabetes	517 (15.6%)	2807 (84.4%)
Cardiovascular Diseases	234 (7.0%)	3090 (93.0%)
B12 Deficiency	110 (3.3%)	3214 (96.7%)
Seizures	44 (1.3%)	3280 (98.7%)
Alcohol Abuse	28 (0.8%)	3296 (99.2%)

Table 3.3: Baseline medication usage of the study subjects

	Yes	No
Antihypertensive agent	1979 (59.5%)	1345 (40.5%)
Lipid-lowering medication	1532 (46.1%)	1792 (53.9%)
Medication for Alzheimer's disease symptoms	560 (16.8%)	2764 (83.2%)
Diabetes medication	419 (12.6%)	2905 (87.4%)

3.3.2 Transition intensity, transition probability, and total length of stay at each state

We included 3,324 MCI patients in the analysis. At the end of the study, 1,326 remained MCI, 1,226 progressed to AD, 721 died without progressing to AD, and 422 died after progressing to AD.

The hazard of moving from MCI to AD was 0.174 (95% CI: 0.164, 0.185) is higher than the hazard of moving from AD to Death (0.123, 95% CI: 0.110, 0.138)(Table 3.4). The probability of transition from Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD) after one year of the initial diagnosis of MCI is 14.9% (Fig 3.2). This probability increases to 41.7% after around six years since the initial MCI diagnosis, followed by a subsequent decrease. The transitional probability to AD for five years and ten years after the initial diagnosis of MCI is estimated to be 40.4%, and 37.8% (Fig 3.2). The probability of remaining as MCI patient after one year, five years, and ten years of initial MCI diagnosis

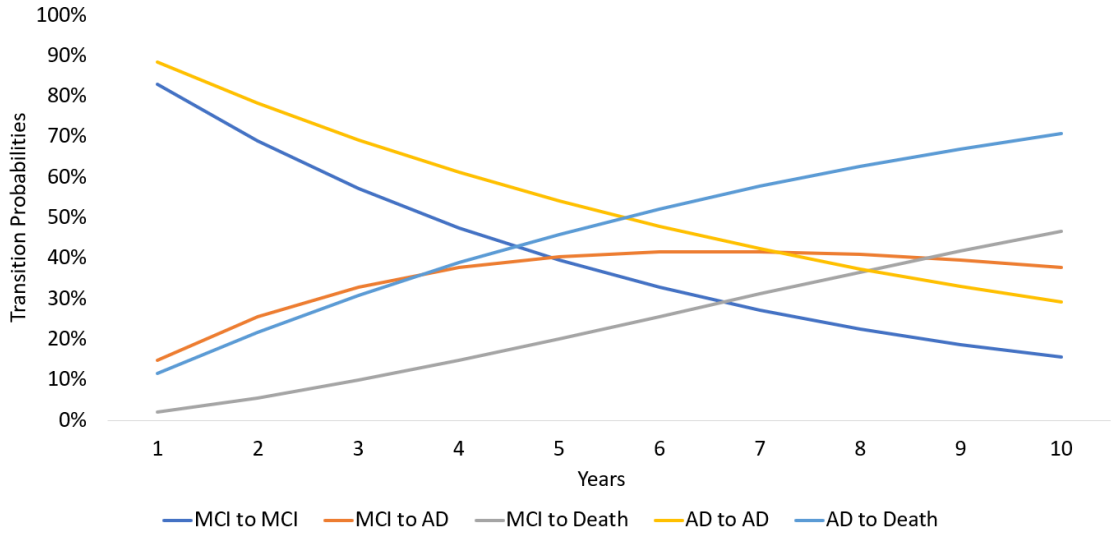
Table 3.4: Transition intensity of Multistate Markov Cox Regression Model

	MCI	AD	Death
MCI	-0.186 (-0.365, -0.095)	0.174 (0.164, 0.185)	0.012 (0.000, 436.056)
AD	NA	-0.123 (-0.138,-0.110)	0.123 (0.110, 0.138)

is 83.0%, 39.5%, and 15.6%, respectively (Figure 2). The probability of dying from MCI after one year, five years, and ten years since the initial diagnosis of MCI is 2.0%, 20.2%, 46.7% (Fig 3.2). The probability of dying from AD, after one year, five years, and ten years of initial AD diagnosis is 11.6%, 45.9%, and 70.8%, respectively (Fig 3.2).

A patient is estimated to spend 5.38 (95% CI: 0.002-6.03) years with MCI, and 7.61 (95% CI: 0.002- 8.88) years with AD after adjusting for demographics, APOE genotype, comorbidities, and the medication usage (Table 3.5).

Figure 3.2: Estimated transition probabilities across 10 years



Year	1	2	3	4	5	6	7	8	9	10
MCI to MCI	83.0%	68.9%	57.2%	47.5%	39.5%	32.8%	27.2%	22.6%	18.8%	15.6%
MCI to AD	14.9%	25.6%	32.9%	37.6%	40.4%	41.7%	41.7%	40.9%	39.5%	37.8%
MCI to Death	2.0%	5.5%	9.9%	14.8%	20.2%	25.7%	31.1%	36.5%	41.7%	46.7%
AD to AD	88.4%	78.2%	69.2%	61.2%	54.1%	47.8%	42.3%	37.4%	33.1%	29.2%
AD to Death	11.6%	21.8%	30.8%	38.8%	45.9%	52.2%	57.7%	62.6%	66.9%	70.8%

Estimated transition probabilities (vertical axis) at year 1 to year 10 (horizontal axis) between states: MCI to MCI (dark blue solid line), MCI to AD (orange solid line), MCI to Death (grey solid line), AD to AD (yellow solid line), AD to Death (light blue solid line).

Table 3.5: Estimated total length of stay at each phase of AD progression

	Total Length of Stay	
State	*Estimate*	*95% CI*
MCI	5.38	(0.002, 6.03)
AD	7.61	(0.002, 8.88)

3.3.3 Effect of medication usage on the risk of progression from MCI to AD

The Multistate Markov Cox Regression model identified that patients with active use of any type of anti-hypertensive agents or lipid-lowering agents were associated with delayed progression of AD, after controlling the demographic, genetic characteristics, and the co-morbidity profile of the patient (Table 3.6).

Patients with active use of any type of anti-hypertensive medication resulted in a trend of 12% reduction in the hazard (HR: 0.88 95%CI:0.75 – 1.02) of transitioning from MCI to AD than those without active use of anti-hypertensive medication (Table 3.6).

Patients with active use of lipid-lowering agents were associated with significantly lower hazards of transitioning from MCI to AD (HR: 0.83, 95%CI:0.71 – 0.96), MCI to Death (HR: 0.51, 95%CI:0.34 – 0.77), and AD to Death (HR: 0.81, 95%CI:0.66 – 0.99) (Table 3.6).

Patients with active use of medication for Alzheimer's disease symptoms demonstrated an elevated hazard (HR: 1.38, 95%CI:1.21 – 1.58) of transitioning from MCI to AD, and no statistically significant association with transitioning from AD to Death (Table 3.6).

Table 3.6: Association of use of medication for known comorbidity risk factors of AD with the risk (HR) of transitioning

Medication	MCI to AD	MCI to Death	AD to Death
Anti-hypertensive agents	0.88 (0.75, 1.02)	1.29 (0.86, 1.94)	0.93 (0.75, 1.15)
Lipid-lowering agents	0.83 (0.71, 0.96)	0.51 (0.34, 0.77)	0.81 (0.66, 0.99)
Medication for Diabetes	1.01 (0.74, 1.37)	1.78 (0.76, 4.13)	1.21 (0.79, 1.87)
Medication for AD Symptoms	1.38 (1.21, 1.58)	0.80 (0.51, 1.23)	1.14 (0.96, 1.36)

3.4 Discussion and Conclusion

Disease progression of AD is a dynamic process and precise prediction of the time course is challenging. Identifying and evaluating factors that may contribute to the progression along the disease trajectory is a critical step toward preventing and diagnosing AD at an early stage and may present opportunities for improved clinical management. In this study, we contribute to the estimation of transition probabilities between stages throughout the AD progression (MCI, AD, and Death) and the lengths of stay for a patient at each stage with large-scale longitudinal data. Different from previous studies, our estimations were adjusted for demographics, APOE genotype, comorbidities, and current medication usage. We also contribute to evaluating the association of active management (with FDA-approved

medications) of several known AD risk factors with the progression of AD. The evaluated medications included antihypertensive agents, lipid-lowering agents, medications for diabetes.

Different from a direct calculation of the "incident" number by the follow-up years, we presented dynamic transition probabilities over the years using the Multistate Markov Cox Regression model. The advantages of this approach are at least three folds: it allows estimating the transition probabilities across multiple states simultaneously; it allows incorporation of covariates and investigation of the hazard of the covariates in the modeling; and it can be implemented to accommodate intermittent observations.

The Multistate Markov Cox Regression model identified that the instantaneous rate of transition from state MCI to state AD (hazard of movement from MCI to AD: 0.174, 95% CI: 0.164, 0.185) is higher than the instantaneous rate of transition from state AD to state Death (hazard of movement from AD to Death: 0.123, 95% CI: 0.110, 0.138). However, the instantaneous rate of transition from state AD to state Death is 10.3 times higher (0.123/0.012) than the instantaneous rate of transition from state MCI to state Death. The estimated time for a patient with MCI was 5.38 (95% CI:0.002-6.03) years, and with AD was 7.61 (95% CI: 0.002-8.88) years. The average life expectancy of AD patients was consistent with previous studies, which suggested that the life expectancy of individuals with Alzheimer's Disease (AD) can range from 3 to 10 years, and those who receive a diagnosis in their 60s and early 70s may anticipate a median lifespan ranging from 7 to 10 years (Zanetti et al., 2009).In a 15-year follow-up study, the mean survival time after the estimated onset of AD was found to be 8.83 years s (95% CI, 8.58–9.07), with males experiencing a shorter survival time of 8.20 years (95% CI, 7.82–8.57) compared to females [9.22 years, (95% CI 8.90–9.53)] (Wattmo et al., 2014). In another 15-year follow-up study, the median survival times were found to be 8.3 years for persons diagnosed of AD at age 65 years, and 3.4 years for persons diagnosed of AD at age 90 years (Brookmeyer et al., 2002).

A recent study identified that intensive blood pressure control reduced the risk of overall MCI, especially for amnestic subtypes of MCI (Gaussoin et al., 2022), which had been postulated to be highly associated with the progression to AD (Palmer et al., 2010). One step further, our study showed that the active use of anti-hypertensive agents for individuals with MCI was associated with a trend of lowering the risk of transition from MCI to AD. Our result highlighted the importance of blood pressure management with anti-hypertensive agents for individuals with mild cognitive impairment in preventing or delaying the onset of AD. Currently, we do not have a clear understanding of the mechanism by which anti-hypertensive agents protect against AD, and how these anti-hypertensive agents contribute to the delay of the pathogenic process of AD. Further, it is not clear whether this effect mainly works by blood pressure-dependent effect or blood pressure-independent effect, or both. Prospective studies on blood pressure-independent effects revealed mixed results (Anderson et al., 2011; Diener et al., 2008; Rouch et al., 2015; Khachaturian et al., 2006; Lebouvier et al., 2020). Several studies and meta-analyses suggested that angiotensin II receptor blockers (ARB) may have superior effects on cognitive function than other anti-hypertensive agents (Anderson et al., 2011; Adesuyan et al., 2022; Hajjar et al., 2012; Yasar et al., 2013; Saavedra, 2016; Ouk et al., 2021). A clear understanding of the underlying mechanism is necessary and important for future work (Rouch et al., 2015).

In addition, our study also identified that the active use of lipid-lowering agents for individuals with MCI had significantly lower hazards of transitioning from MCI to AD, MCI to Death, and Ad to Death. The result suggested an overall benefit of cholesterol management with lipid-lowering agents for individuals with MCI. The active use of lipid-lowering agents is not only associated with prolonged survival time against AD but also prolonged survival time against death. The association between cholesterol levels and AD remains complicated. It is not clear whether this effect mainly works by its effect on the brain or circulating cholesterol metabolism, or both (Puglielli et al., 2003). It is anticipated that acute treatment with statins is unlikely to affect brain homeostasis over a short period of time or

improve cognitive function. Several studies revealed a positive association between low levels of circulating low-density lipoprotein cholesterol (LDL-C) and cognitive decline, as well as the risk of AD (Zhou et al., 2020; Wingo et al., 2019; Iwagami et al., 2021; Hua et al., 2021). Recnet findings implicated LDL-C in the pathophysiology processes of AD independent of APOE (Cheng et al., 2020; Wingo et al., 2022).

Unsurprisingly, we observed an elevated hazard of progression to AD for patients with the active use of medication for Alzheimer's disease symptoms. Practitioners could prescribe medication for Alzheimer's symptoms in MCI patients to alleviate memory issues before an AD diagnosis, especially in AD-like or amnestic MCI cases. Therefore, patients with MCI who are suspected of AD (treated with medication for Alzheimer's disease symptoms) were observed to be associated with a higher hazard of transitioning to AD.

We didn't observe any significant association between the active use of medication for Alzheimer's disease symptoms and delayed progression from AD to death. Since all medications for Alzheimer's disease that we investigated during the study period were approved for reducing or controlling some cognitive and behavioral symptoms but tackling the underlying pathology in the disease (during the study period), it is still unclear whether those medications for mitigating Alzheimer's disease symptoms had an effect on prolonging the survival time of patients with Alzheimer's disease.

This study had several limitations. First, we did not have sufficient brain imaging or biomarker data that would have helped support the accuracy of the clinical diagnosis of MCI or AD. Second, we investigate the general use of medications among the study cohort, heterogeneousness may exist within each medication category. Future studies could be carried out to differentiate anti-hypertensive/lipid-lowering agents by classes or chemical properties, etc. Third, the Multistate Markov model of this analysis is a time-homogeneous model, which assumes a constant instantaneous transition rate for each transition. It may be possible that the progression of the disease is not constant throughout the disease.

Despite these limitations, our study provides insights regarding patients who transitioned from MCI to AD, MCI to Death, and AD to Death on a clinical-based cohort, and future studies could be carried out in population-based studies.

Chapter 4

Multi-state survival models with noisy healthcare survival data

4.1 Introduction

Diagnosis is a highly complex task(Schildkrout, 2018). Missed, delayed, or wrong diagnoses are inevitable in the healthcare system, especially in the primary care setting where a high volume of diagnostic decisions was made in a complex and uncertain environment(Singh et al., 2017; Kostopoulou et al., 2008). And those diagnostic errors could bring serious consequences to the patients and the healthcare system. A report from the National Academy of Medicine (NAM) showed that "most people will experience at least one diagnostic error in their lifetime, sometimes with devastating consequences" (National Academies of Sciences et al., 2015). For multiple reasons, diagnostic errors are relatively common in primary care practices (Singh et al., 2013). A recent study demonstrated that missed vascular events, infections, and cancers account for nearly 75% of serious harms from diagnostic errors (Newman-Toker et al., 2021). Diseases like Alzheimer's' appear to have higher diagnostic errors due to the complication of the disease and the limited use of advanced measurements in primary care practices (Weller and Budson, 2018). As such, understanding the performance of an algorithm under a high-noise environment is crucial.

The analysis of survival data with noise continues to garner attention in the field of Big Data, as it presents challenges not encountered in traditional survival data due to the availability of high-dimensional data. Within the framework of Cox-like regression-based survival analysis, previous studies have explored the implications of error-contaminated covariates and put forward methodologies to address this concern.

Several studies have been dedicated to investigating the influence of measurement error on the estimation of survival probabilities and hazard ratios. Rosner et al. (1990) conducted a simulation study to explore the impact of measurement error on hazard ratio estimation in Cox regression. Their findings revealed an escalating bias in the hazard ratio estimate as the measurement error in the covariate increased. Additionally, the magnitude of the bias was found to be contingent on the correlation between the covariate and survival time. Another investigation by Hall (2008) examined the consequences of measurement error on the estimation of survival probabilities and hazard ratios in the presence of random censoring. Their study demonstrated that measurement error in the covariate could introduce bias into the estimates of survival probabilities and hazard ratios. Moreover, the extent of the bias was influenced by the correlation between the covariate and survival time. Furthermore, Küchenhoff et al. (2007) delved into the impact of Berkson measurement error on the estimation of the slope parameter in Cox proportional hazard models. The researchers employed graphical methods and a simulation study to analyze the measurement error within the context of the German Uranium Miners Cohort Study. They discovered that minor measurement errors and infrequent disease cases did not exhibit substantial bias, even in the presence of high variance in the Berkson measurement error. However, the effect of multiplicative measurement error yielded more pronounced consequences (Küchenhoff et al., 2007).

A range of approaches has been proposed to address noisy covariates from multiple perspectives. Some models suggest applying various penalty methods to select only the active

variables while suppressing the inactive covariates that inadequately explain the survival data (Fan and Li, 2002; Yan and Huang, 2012; Huang et al., 2013; Cai et al., 2005). Other approaches focus on detecting and addressing measurement error or calibrating the estimation of model parameters using inference methods (Huang and Wang, 2000; Xie et al., 2001; Song and Huang, 2005; Grace and Lawless, 2007; Zhao and Prentice, 2014). More recently, there has been a growing interest in incorporating network structures among high-dimensional covariates into the modeling procedure (Chen and Yi, 2020; Zhang, 2020).

Previous research has extensively discussed estimation strategies addressing measurement errors in the variable of interest and the censoring variable. Chan et al. (2018) employed a semi-parametric transformation (ST) failure time model, combining surrogate measures of ICD coding and the first natural language processing (NLP) mention of a disease-related term in doctor's notes, to estimate the true survival time. Additionally, several deconvolution strategies, including wavelet-based methods, have been proposed for estimating probability density functions or cumulative distribution functions in the presence of measurement error (Antoniadis et al., 1999; Li, 2002; Wu and Wells, 2003; Brunel-Piccinini and Comte, 2005; Comte et al., 2018; Mohammed and Hussein, 2019). These approaches center around the utilization of Wavelet Transform (WT) to effectively remove noise from the data.

The impact of measurement errors in dependent variables on multi-state survival modeling, particularly in the context of disease progression prediction in Alzheimer's Disease (AD), has received limited attention in the existing literature. In this chapter, we delve into the robustness of multi-state survival models in the presence of a noisy dependent variable, aiming to evaluate their performance in predicting the progression of AD. Our focus is on addressing the challenges posed by variability and delayed diagnosis in AD, as timely and accurate diagnosis of AD can be particularly challenging. Hence, selecting a model that exhibits superior performance in a noisy setting becomes paramount in this context.

4.2 Model Setup

4.3 Data Simulation

Simulated data sets were generated to evaluate the performance of the two algorithms. To do so, we first simulated 30 sets of datasets (30 set*4 scenarios) of each consisting of 5000 individual trajectories following the three-state model structure shown in Figure 1. The model comprises two transient states and one absorbing state, with no provision for backward transitions due to the aggressive and irreversible nature of Alzheimer's disease.

Then, to simulate the transitions (time to transit), sojourn times were generated from a Weibull distribution, which is characterized by a probability density function:

$$f_{i,j}(t) = (\frac{k_{i,j}}{\lambda_{i,j}})(\frac{t}{\lambda_{i,j}})^{(k_{i,j-1})} exp\ (-(\frac{t}{\lambda_{i,j}})^{k_{i,j}}) \tag{4.1}$$

Where i=1,2,j=2,3,$i \neq j$, $\lambda_{i,j}$ is the scale parameter, and $k_{i,j}$ is the shape parameter.

All parameters were selected based on the real data from NACC (National Alzheimer's Coordinating Center) during the period between September 2005 and May 2021. The model included age as a covariate. In order to account for the potential effect of age on the sojourn times between states, distinct values of scale and shape parameters of Weibull distribution were deployed for each transition with parameterization based on age. In order to accomplish this, patient trajectories associated with each transition at different age brackets were selected from the NACC cohort. The data was partitioned into brackets of five-year increments for each transition, beginning from the age of 60. Subsequently, a linear regression was fitted with the NACC cohort to parametrize the scale and shape parameters based on age.

Following the creation of 30 initial simulated datasets to represent error-free conditions,

an additional 90 datasets were generated to incorporate diagnostic errors at varying levels. Three distinct scenarios were simulated, each involving random errors at rates of 10%, 20%, and 30%. The diagnostic errors were modeled as delayed diagnoses, following a normal distribution with a mean of 0.75 years (9 months) and a standard deviation of 0.5 years (6 months).

4.4 Multistate Markov model

In Section 3.24, titled "Multi-State Markov Model," we presented the equations for transition probabilities at a given time point within the assumption of time-homogeneous for a three-state illness model (equation 3.4 - 3.12). These transition probabilities were derived using the Kolmogorov equation, which provides a framework for obtaining them through the transition intensity matrix. Building upon this foundation, we now delve into further elucidating the intricacies of the Kolmogorov equation and the transformation process between the transition intensity matrix and the transition probability matrix. This section offers a comprehensive understanding of these key aspects and lays the foundation for comparing the classic Multistate Markov model and the Multistate ODEs.

In a continuous-time Markov chain, the transition probability from state i at time s to state j at time t can be expressed using the transition rates $q_{k,j}(t)$. This relationship is governed by the Kolmogorov forward and backward equations, which take the following form:

$$\frac{\partial p_{i,j}(s,t)}{\partial t} = \Sigma_k p_{i,k}(s,t) q_{k,j}(t) \tag{4.2}$$

$$\frac{\partial p_{i,j}(s,t)}{\partial s} = -\Sigma_k p_{k,j}(s,t) q_{i,k}(s) \tag{4.3}$$

When assuming time-homogeneity, the transition matrix remains constant throughout the

entire process, representing a special case where the transition matrix is invariant and does not vary with time, with the following form:

$$\frac{\partial p_{i,j}(s,t)}{\partial t} = \Sigma_k p_{i,k}(s,t) q_{k,j} \tag{4.4}$$

$$\frac{\partial p_{i,j}(s,t)}{\partial s} = -\Sigma_k p_{i,k}(s,t) q_{k,j} \tag{4.5}$$

The Kolmogorov equations can be conveniently represented in a matrix form, as follows:

$$\frac{\partial P(t)}{\partial t} = P(t)Q(t) \tag{4.6}$$

$$\frac{\partial P(t)}{\partial t} = Q(t)P(t) \tag{4.7}$$

,Where [P(t)] (for each t> 0) is an M by M matrix whose i, j element is $p_{i,j}(t)$ and [Q(t)] is an M by M transition rate matrix whose i, j element is $q_{i,j}(t)$ for each $i \neq j$ and - $\Sigma_{j \neq i} q_{i,j}$ for $i = j$.

Under the time-homogeneity assumption, we have:

$$\frac{\partial P(t)}{\partial t} = P(t)Q \tag{4.8}$$

$$\frac{\partial P(t)}{\partial t} = QP(t) \tag{4.9}$$

Therefore, we have:

$$P(t) = e^{tQ} \tag{4.10}$$

4.5 Multistate ODEs model

Rather than assuming a constant transition matrix over time, the Multistate ordinary ODEs adopt a time-varying approach by modeling the transition matrix using a neural network(Groha et al., 2020). Furthermore, Multistate ODEs also incorporate the history of the evolution and the covariate of the individual into the neural network by introducing an auxiliary memory states m(t), governed by the differential equation(Groha et al., 2020):

$$\frac{\partial m_i}{\partial t} = M_i(t, P(t), m(t)) \tag{4.11}$$

Then, the Kolmogorov equations can be written as:

$$\frac{\partial p_{i,j}(0,t)}{\partial t} = \Sigma_k p_{i,k}(0,t) q_{k,j}(t, P(0,t)(t), m(t)) \tag{4.12}$$

$$\frac{\partial p_{i,j}(s,0)}{\partial s} = -\Sigma_k p_{k,j}(s,0) q_{i,k}(s, P(0,s), m(t)) \tag{4.13}$$

Both $q_{i,j}(t, P(0,t)(t), m(t))$ and $M_i(t, P(t), m(t))$ were modeled with neural networks, where the first q outputs (q number of non-zero off-diagonal elements of Q) of the last layer are passed through a softplus non-linearity. The application of the softplus non-linearity function served as a constraint, ensuring that all the transition rates remained strictly greater than zero.

The dynamics of the system, encompassing the Kolmogorov equations (equations 4.12 and 4.13) and the auxiliary memory states m(t) accounting for covariates and past history (equation 4.11), were formulated as ordinary differential equations. To facilitate training, the gradient of the neural network was acquired by performing backpropagation through the ordinary differential equation (ODE) solver. This approach enabled the efficient and effective

optimization of the neural network parameters while considering the underlying dynamics described by the differential equations. The original algorithm is shown in (Fig 4.1).

Figure 4.1: The algorithm of Multistate ODEs

Algorithm Obtain $P_{ij}(s,t)$ and $q_{ij}(t)$ in SURVNODE

Input: Covariates $\boldsymbol{x}$, time interval (s,t).

$\boldsymbol{m}(0) = f_\theta(x)$, $\boldsymbol{P}(0,0) = \mathbb{1} \rightarrow s_0 = (\boldsymbol{P}(0,0), \boldsymbol{P}(0,0), \boldsymbol{m}(0))$ ▷ Get initial values.

def KFE_KBE($\boldsymbol{P}(0,t), \boldsymbol{P}(t,0), \boldsymbol{m}(t), t$): ▷ Kolmogorov forward and backward equation.

$q_{ij}(t),\ M_i(t) = g_\phi(\boldsymbol{P}(0,t), \boldsymbol{m}(t), t)$ ▷ λ, M from NN with `softplus` for q.

$q_{ii} = -\sum_k q_{ik}$ ▷ Enforce constraints.

$\frac{\mathrm{d}P_{ij}(0,t)}{\mathrm{d}t} = \sum_k P_{ik}(0,t) q_{kj}$ ▷ Calculate gradient for Kolmogorov forward equation.

$\frac{\mathrm{d}P_{ij}(t,0)}{\mathrm{d}t} = -\sum_k q_{ik} P_{kj}(t,0)$ ▷ Calculate gradient for Kolmogorov backward equation.

$\frac{\mathrm{d}m_i(t)}{\mathrm{d}t} = M_i(t)$ ▷ Calculate gradient for augmented evolution.

return $\left[\frac{\mathrm{d}P_{ij}(0,t)}{\mathrm{d}t}, \frac{\mathrm{d}P_{ij}(t,0)}{\mathrm{d}t}, \frac{\mathrm{d}m_i(t)}{\mathrm{d}t}\right]$ ▷ return derivatives

$\boldsymbol{P}(0,t), \boldsymbol{P}(s,0), \boldsymbol{m}(t), \cdots = \mathtt{ODEsolve}(s_0, \mathtt{KFE\_KBE}, (0,t), \mathtt{save\_at} = \{s,t\})$

$q_{ij}(t) = g_\phi(\boldsymbol{P}(0,t), \boldsymbol{m}(t), t)$ ▷ Get the instantaneous transition rate.

$\boldsymbol{P}(s,t) = \boldsymbol{P}(s,0) \cdot \boldsymbol{P}(0,t)$ ▷ Use the composability to get $\boldsymbol{P}(s,t)$

return $P_{ij}(s,t)$, $q_{ij}(t)$

4.6 Evaluation Metric

In adherence to the methodology proposed by Titman and Sharples (2008), we computed an indicator to estimate the level of the data divergence from the predicted patterns of the Markov model. This involved a comparison between the observed count (O_{ir}) and the expected count (E_{ir}) within the context of the fitted Markov model for a specific state (r) at a given time point t_i.

To evaluate the overall model deviation, we performed these calculations for a time span encompassing t=1, 2, 3, and up to 30. By summing the individual deviations across all the assessed time points, ranging from t=1 to 30, we obtained the total deviation of the model

as an overall measure of the goodness of fit.

$$M = \Sigma_{i=1}^{30} \frac{(O_{ir} - E_{ir})^2}{E_{ir}}$$

, where M is the total deviation from the estimated model, O_{ir} is the observed counts at time t_i at state r, and E_{ir} is the predicted counts at time t_i at state r.

Furthermore, we computed the mean and standard deviation across 30 experiments for both models. Subsequently, we conducted t-tests and f-tests to assess potential significant differences in the mean and variance of the total deviation between the two models. The p-values of the t-test and f-test were reported in the result section. An additional series of t-tests were carried out to elucidate potential differences (increase/decrease) in the total deviations of the models at various noisy levels. This investigation aims to provide a comprehensive understanding of the behavior of the models under different noise conditions.

4.7 Result

Multistate Neural ODEs demonstrated a similar mean total deviation to the Multistate Markov model under conditions of no random error (P-value: 0.671), 10% random error (P-value: 0.689), and 20% random error (P-value: 0.122) (Table 4.1, Fig 4.2). However, in the presence of 30% random error, Multistate Neural ODEs exhibit a significantly higher mean total deviation (P-value $<$ 0.001) (Table 4.1, Fig 4.2).

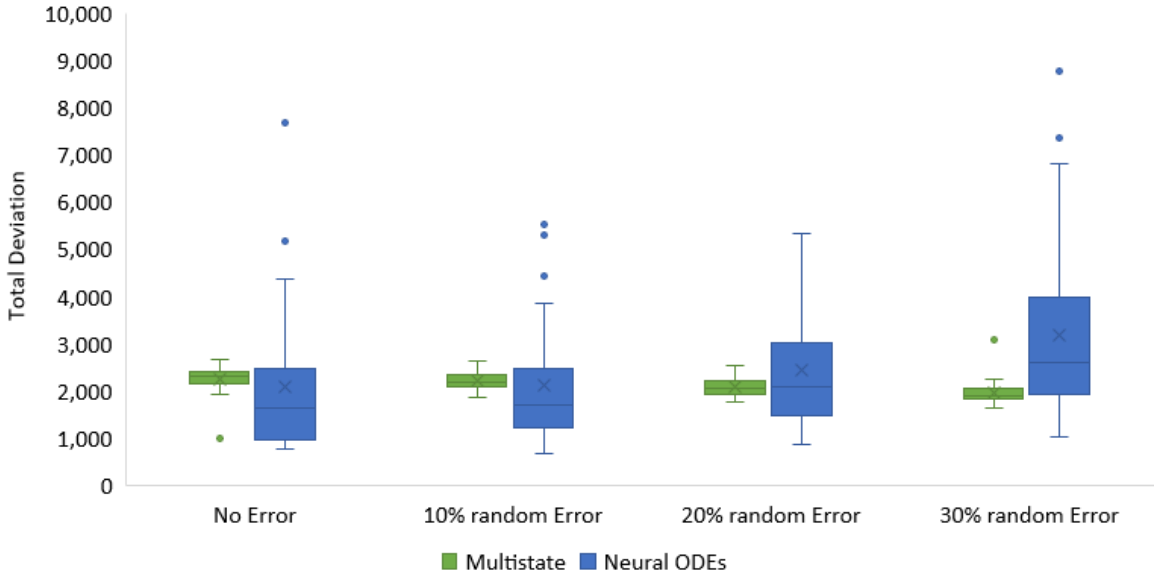
Table 4.1: Model comparison: mean and variance differences in the total deviation measure between Multistate Markov and Multistate Neural ODEs

Scenario	Multistate, Mean(SD)	Neural ODEs. Mean(SD)	T-test	F-test
No Error	2320.86 (343.11)	2198.06 (1528.96)	0.671	<0.01
10% random Error	2217.79 (187.32)	2120.68 (1303.58)	0.689	<0.01
20% random Error	2082.23 (198.07)	2438.59 (1210.19)	0.122	<0.01
30% random Error	1964.69 (264.60)	3188.07 (1941.27)	0.002	<0.01

Table 4.2: Model comparison: mean differences in the total deviation measure across noisy levels

Differences in mean (t-test)		
Comparison	Multistate	Neural ODEs
No Error vs 10% random Error	0.154	0.834
No Error vs 20% random Error	0.002	0.502
No Error vs 30% random Error	0.000	0.032

Figure 4.2: Distributions of the total deviation measure for Multistate Markov and Multistate Neural ODEs across noisy levels



The Multistate Markov model revealed a trend of decreasing in total deviations as the level of random error increases. No significant difference was observed in mean total deviations between no error and 10% random error conditions (P-value: 0.154) (Table 4.2, Fig 4.2). However, significant differences were observed between the 20% random error (P-value: 0.002) and 30% random error (P-value: < 0.001) conditions compared to the no error condition (Table 4.2, Fig 4.2).

There were no significant differences observed in the mean total deviations of Multistate

Neural ODEs between the no error condition and either the 10% random error (P-value: 0.834) or 20% random error conditions (P-value: 0.502) (Table 2, Fig 1). However, a higher mean total deviation was observed for the 30% random error (P-value: 0.032) condition compared to the no error condition (Table 4.2, Fig 4.2).

It is worth noting that the case of Multistate Neural ODEs exhibits several extreme values of total deviations (Fig 4.2).

4.8 Discussion

Our analysis revealed that the Multistate Neural ODEs tended to have a slightly better fit (although the differences are not statistically significant) under lower noise level conditions (the absence of random error and the 10% random error condition) in comparison to higher noise level circumstances (especially, the 20% random error condition and the 30% random error condition). With increasing noise levels, the Multistate Markov model demonstrated superior performance compared to the Multistate Neural ODEs model. Significantly lower total mean total deviations were observed under the random error level of 20% and 30% when compared with the Multistate Neural ODEs.

The Multistate Markov model exhibited a relatively stable mean total deviation across varying levels of error in the dependent variable. Specifically, as the level of error increased, the mean total deviation remained relatively consistent, with a notable trend toward a decline in the mean total deviation.

Besides, the Multistate Markov model also consistently exhibited a lower standard deviation of total deviations across all 30 experiments, in comparison to the Multistate Neural ODEs, irrespective of the noise error conditions. This finding suggests that the Multistate Markov model may be more robust in handling noise and variability in the dependent variable, thus offering a more reliable and consistent performance across a range of conditions.

The presence of outliers of total deviation under Multistate Neural ODEs may indicate limitations or weaknesses in the model's ability to handle specific scenarios or data patterns or indicate overfittings to the feeding data.

The comparison between the two models sheds light on the well-known bias-variance dilemma in statistics and machine learning, and the two sources of error, i.e., bias and variance(Kohavi et al., 1996; Geman et al., 1992; Friedman, 1997). The bias error is an error from erroneous assumptions in the modeling process, leading to deviations from the accurate representation of underlying patterns or relationships. The variance error arises as a consequence of the model's susceptibility to even minor fluctuations within the training set. High variance can be attributed to the algorithm's inclination to capture and model the random noise present in the training data, thereby resulting in a less robust and more volatile predictive performance.

The classic Multistate Markov model relies on the time-homogeneous assumption, assuming a consistent transition rate throughout time. Nevertheless, it is essential to recognize that this assumption has the potential to introduce bias into the model.

The Multistate Neural ODEs circumvent the need for imposing such assumptions by incorporating a neural network that estimates the time-varying transition intensity. The enhanced model complexity enables it to capture nuanced variations in the data, which may lead to overfitting. As the level of error increases, the performance of the Multistate Neural ODEs is compromised.

In the context of the dependent variable error-containing environment, our study reveals that the classic Multistate Markov model demonstrates greater robustness when compared to the Multistate Neural ODEs, especially in the presence of high-level noise.

Our finding highlights the relative strengths and weaknesses of each model and underscores the importance of carefully considering the specific application and operating conditions

when selecting the appropriate modeling approach.

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