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EVALUATING THE IMPACTS OF ANTIDEPRESSANT USE ON THE RISK OF DEMENTIA

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EVALUATING THE IMPACTS OF ANTIDEPRESSANT USE ON THE RISK OF DEMENTIA

DISSERTATION

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

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ABSTRACT OF DISSERTATION

EVALUATING THE IMPACTS OF ANTIDEPRESSANT USE ON THE RISK OF DEMENTIA

Dementia is a clinical syndrome caused by neurodegeneration or cerebrovascular injury[1]. Patients with dementia suffer from deterioration in memory, thinking, behavior and the ability to perform everyday activities[2]. Since there are no cures or disease-modifying therapies for dementia[3,4], there is much interest in identifying modifiable risk factors that may help prevent or slow the progression of cognitive decline[4,5]. Medications are a common focus of this type of research.[6,7]

Importantly, according to a report from the Centers for Disease Control and Prevention (CDC), 19.1% of the population aged 60 and over report taking antidepressants during 2011-2014, and this number tends to increase[8]. However, antidepressant use among the elderly may be concerning because of the potentially harmful effects on cognition[9-12]. To assess the impacts of antidepressants on the risk of dementia, we conducted three consecutive projects.

In the first project, a retrospective cohort study using Marginal Structural Cox Proportional Hazards regression model with Inverse Probability Weighting (IPW) was conducted to evaluate the average causal effects of different classes of antidepressant on the risk of dementia. Potential causal effects of selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), atypical anti-depressants (AAs) and tri-cyclic antidepressants (TCAs) on the risk of dementia were observed at the 0.05 significance level. Multiple sensitivity analyses supported these findings.

Unmeasured confounding is a threat to the validity of causal inference methods. In evaluating the effects of antidepressants, it is important to consider how common comorbidities of depression, such as sleep disorders, may affect both the exposure to anti-depressants and the onset of cognitive impairment. In this dissertation, sleep apnea and rapid-eye-movement behavior disorder (RBD) were unmeasured and thus uncontrolled confounders for the association between antidepressant use and the risk of dementia. In the second project, a bias factor formula for two binary unmeasured confounders was derived in order to account for these variables. Monte Carlo analysis was implemented to estimate the distribution of the bias factor for each class of antidepressant. The effects of antidepressants on the risk of dementia adjusted for both measured and unmeasured

confounders were estimated. Sleep apnea and RBD attenuated the effect estimates for SSRI, SNRI and AA on the risk of dementia.

In the third project, to account for potential time-varying confounding and observed time-varying treatment, a multi-state Markov chain with three transient states (normal cognition, mild cognitive impairment (MCI), and impaired but not MCI) and two absorbing states (dementia and death) was performed to estimate the probabilities of moving between finite and mutually exclusive cognitive state. This analysis also allowed participants to recover from mild impairments (i.e., mild cognitive impairment, impaired but not MCI) to normal cognition, and accounted for the competing risk of death prior to dementia. These findings supported the results of the main analysis in the first project.

KEYWORDS: dementia, antidepressants, inverse probability weighting, unmeasured confounding, multi-state Markov chain

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04/15/2019

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DEDICATION

To my motherland and my family.

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CHAPTER ONE. INTRODUCTION

1.1. Dementia

Dementia, which includes Alzheimer's disease, vascular dementia, Lewy body disease and frontotemporal dementia, is a clinical syndrome caused by neurodegeneration or cerebrovascular injury[1]. Patients with dementia suffer from deterioration in memory, thinking, behavior and the ability to perform everyday activities[2].

In recent years, dementia has become an important public health topic worldwide due to its increasing prevalence in an aging society[2]. In the United States, the population age 65 and older is estimated to be 53 million in 2018[13], and this number is still increasing[14]. The number of Americans age 65 and older with Alzheimer's or a related dementia in 2018 is estimated to be 5.5 million[13]. In other words, one in ten Americans age 65 and older has dementia.

Dementia is known to be associated with extremely heavy burden on families and communities. It has been estimated that the yearly monetary cost per person attributable to dementia was between $41,689 and $56,290, depending on the method used to value informal care[15]. Therefore, the total monetary cost of dementia in 2010 has been estimated to be between $157 billion and $215 billion[15].

As there are no cures or disease-modifying therapies available for any disease that causes dementia[3,4], there is major interest in identifying modifiable risk factors for dementia[4,5], such as life style factors, medication use[6,7], and comorbid health conditions[16]. In this dissertation, we will be focusing on antidepressant use.

1.2. Antidepressants

Antidepressants are widely used among the elderly. According to a report from the Centers for Disease Control and Prevention (CDC), 19.1% of the population aged 60 and over reported taking antidepressants during 2011-2014, and this number tends to increase[8]. Besides treating depression, antidepressants have been used for treating other psychiatric disorders, such as anxiety, serious phobias, and post-trauma stress disorder[17-20]. In some cases antidepressants can be used for treating long-term pain[21]. which is a common health condition among the elderly.

However, antidepressant use among the elderly may be concerning because of the impacts of the underlying age-related pharmacokinetic and pharmacodynamic safety issues and potentially harmful drug-drug interactions on cognition[22,23]. For example, evidence has suggested that tri-cyclic antidepressants (TCAs) may increase the risk of cardiac arrhythmia and should be avoided for the elderly who are at high risk of cardiovascular diseases[22,24], which is a risk factor for dementia. Another study suggests that combined use of antidepressants and NSAIDs is associated with an increased risk of intracranial hemorrhage within 30 days of initial combination[25]. More importantly, the conclusions regarding the effects of antidepressants on the risk of dementia are inconsistent[26-28]. Thus, the use of antidepressants among the geriatric population is a critical but under-investigated public health topic.

1.3. Causal Inference for Observational Studies in Pharmacoepidemiology

Ideally, the causal effects of treatments on outcomes should be investigated in a randomized study so that trial arms are exchangeable groups and the differences in

outcomes reflect the effects of the treatment rather than differences in participant characteristics[29]. However, randomized studies are not always feasible in real life, since some treatments cannot be randomized due to ethical considerations, and sometimes it is difficult to conduct head-to-head trials. If the subjects select their own treatments or the treatments are assigned to them by clinical professionals, the differences in outcomes may due to selection bias and confounding rather than the effects of the treatments[29].

For observational studies in pharmacoepidemiology, people may be interested in the average causal effects of a certain medication on a well-defined population. Hernán and Robins defined that an average causal effect of treatment A on outcome Y is present if $E[Y^{a=1}] \neq E[Y^{a=0}]$, where Y^a is the counterfactual outcome under a given treatment regimen A=a[30]. In other words, there is a causal effect of the treatment when the same population is observed under treatment and no treatment, and experiences a different outcome under each. In randomized trials, the treatment arms are assumed to be exchangeable (i.e., it doesn't matter which group receives which treatment; the effects of the treatment should be the same in any group randomly assigned to that treatment), and thus causal effects are identifiable. Causal inference methods facilitate using observational data to determine the average causal effect by simulating randomized treatment assignment.

Analytically the population average causal effects of a treatment can be estimated by Marginal Structural Models with Inverse Probability Weighting (IPW) estimator, given that the assumptions of conditional exchangeability, positivity, consistency, and correct model specification are satisfied[30]. IPW creates a pseudo-population in which the initiation of the treatment is not related to the measured confounders; to interpret the IPW

estimates as causal effects, we must assume there is no unmeasured confounding[30]. In such a pseudo-population, the average causal effects of the treatments on the outcomes can be estimated by regressing the outcome on the treatment using a marginal structural model, which is a conventional regression model weighted by IPW[31].

The traditional approach to adjust for confounding is to include confounders as covariates in a multiple regression model[32]. However, recent advances in epidemiological methods have shown that the traditional approach is often inadequate[32,33]. Greenland et al. suggested that the major drawback of the traditional approach to adjusting for confounders using statistical models is that they need many parametric assumptions that are not known to be correct or may be incorrect[33]. Therefore, in a high-dimensional study with many covariates and multi-group treatment, causal diagrams, such as Directed Acyclic Graphs (DAGs), can be used to identify a minimal sufficient set of adjustment variables that confound the effects of treatments on the outcomes by depicting a set of hypotheses about the causal process[29].

One of the key assumptions for causal inference in epidemiology is that there should not be any unmeasured confounding. Nevertheless, this assumption is often violated in observational studies. When unmeasured confounding exists but fails to be controlled for, the estimated treatment effects may be biased[34]. Monte Carlo Sensitivity Analysis could be used to adjust the data by estimating the sensitivity parameters for the omitted sources of uncontrolled confounding[35].

1.4. About this Research

The goal of this research is to investigate the causal effects of different classes of antidepressant medications on the risk of dementia using causal inference strategies. Data were obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). We hypothesize that antidepressant use among the elderly may increase the risk of dementia, and the impacts may be heterogeneous for different classes of antidepressant.

In Chapter Two, a new user design retrospective cohort study was conducted to evaluate the causal effects of different classes of antidepressant on the risk of dementia by performing a Marginal Structural Cox Proportional Hazard Regression Model with an Inverse Probability Weighting estimator. Sensitivity analyses were conducted to assess the robustness of the main analysis results.

In Chapter Three, the impacts of unmeasured confounders were assessed. Unmeasured confounding is a threat to the validity of causal inference methods. In evaluating the effects of anti-depressants, it is important to consider how common comorbidities of depression, such as sleep disorders, may affect both the exposure to anti-depressants and the onset of cognitive impairment. In this dissertation, sleep apnea and rapid-eye-movement behavior disorder (RBD) were identified as confounders by our hypothesized causal model but were unmeasured and thus uncontrolled confounders for the association between antidepressant use and the risk of dementia. A bias factor formula for two binary unmeasured confounders was derived in order to account for these variables. Monte Carlo analysis was implemented to estimate the distribution of the bias

factor for each class of antidepressant. The effects of antidepressants on the risk of dementia adjusted for both measured and unmeasured confounders were estimated.

In Chapter Four, a multi-state Markov chain with three transient states (normal cognition, impaired but not MCI, and MCI) and two absorbing states (dementia and death prior to dementia) was built to account for changes in treatment over time and time-varying covariates. A series of multinomial logistic regression models were constructed to model the log-odds of transitions between any two transient states and transitions between a transient state and an absorbing state. The long-run behavior of the chain was also evaluated.

Finally, a conclusion of this research and discussion of directions for future studies can be found in Chapter Five.

CHAPTER TWO. THE EFFECTS OF ANTIDEPRESSANT USE ON THE RISK OF DEMENTIA: A RETROSPECTIVE COHORT STUDY

2.1. Introduction

Dementia has become a significant public health issue worldwide in recent years[2]. Patients with dementia suffer from deterioration in memory, thinking, behavior and the ability to perform everyday activities[1]. The prevalence of age-related dementia in the United States in 2010 is estimated to be 14.7% for those aged 70 or older[36]. Since there are no cures or disease-modifying therapies for dementia[3,4], there is much interest in identifying modifiable risk factors that may help prevent or slow the progression of cognitive decline[4,5]. Medications are a common focus of this type of research[6,7], and antidepressant use is a possible modifiable risk factor in the geriatric population. Importantly, according to a report from the Centers for Disease Control and Prevention (CDC), 19.1% of the population aged 60 and over report taking antidepressants during 2011-2014[8]. In other words, one fifths of this population were using antidepressants.

Antidepressants can be identified based on their mechanisms of action: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tri-cyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants (AAs). All these antidepressants work to increase the levels of one or more of the neurotransmitters in the patient's body—serotonin, norepinephrine, or dopamine—but different classes of drugs achieve this goal very differently[37].

SSRIs help to reduce symptoms of depression through increasing the amount of serotonin by blocking the re-absorption of serotonin in the brain[38]. SNRIs differ from SSRIs in that SNRIs increase the levels of two neurotransmitters: serotonin and

norepinephrine[39]. TCAs were one of the earliest antidepressants developed, and they will also increase the levels of serotonin and norepinephrine[40]. However, TCAs lead to more side effects compared to SSRIs and SNRIs, because TCAs will simultaneously impact other chemicals in the human brain[41]. MAOIs function by preventing monoamine oxidase, an enzyme, from removing serotonin, norepinephrine, and dopamine so that the levels of these neurotransmitters are maintained in brain[42]. MAOI users also report more side effects compared to SSRI or SNRI users due to MAOI's impact on other neurotransmitters and the digestive system[43]. AAs work through novel mechanisms of action, but in general they also elevate the levels of serotonin, norepinephrine, or dopamine[44,45].

According to guidelines of the National Health Services (NHS) in England[46], when antidepressant therapy is necessary, SSRIs are normally considered as the first-line treatment; other classes of antidepressants are generally used as second-line or third-line treatment. A combination of two different classes should be initiated by specialists only. However, it should be noted that the selection of a particular medication for a particular patient depends on a variety of factors, such as the avoidance of specific side effects and the presence of comorbidities, so there is not one antidepressant medication that is clearly more effective than another at the population level[47].

No strong conclusions can be made from current studies focusing on the relationship between antidepressant use and dementia. First, different antidepressants work via different mechanisms of action, and there are very few studies comparing the potential heterogeneous effects of antidepressant classes on the risk of dementia among the elderly[48,49]. Second, the geriatric population is usually under-represented in clinical

trials, thus the effects of antidepressants on the elderly in settings where causal inference is straightforward remain under-investigated[50]. Finally, existing studies investigating the effects of antidepressants made inconsistent conclusions. Some *in vivo* studies showed that chronic SSRI treatment reduces amyloid-β accumulation, which is a marker for Alzheimer's disease, in mice, and this benefit also appears to be true in humans[26-28]. However, a randomized, placebo-controlled, double-blind, parallel group clinical trial study showed that fluoxetine, a commonly used SSRI, is associated with worsening cognitive functions[51]. A cross-over clinical study focusing on the effect of SNRI on memory and mental processing speed concluded that SNRIs may improve memory, mental processing speed and motor performance[52], but a large cohort study suggests that SNRI use is associated with increased risk for dementia[51]. Some AAs, such as amitriptyline, dothiepin, mianserin, and trazodone, may impair attention and ability to concentrate[53]. Yet, another study recommends that AAs are preferable in the elderly patients because use of risperidone, a type of AA, in Alzheimer's disease subjects did not result in a significant reduction in MMSE score over a 12-week period compared with placebo group, while a lower rate of adverse events was observed[54]. With inconsistent information, it is difficult to draw any conclusions regarding the impacts of antidepressants on the risk of dementia.

To summarize previous studies on human subjects investigating the relationship between antidepressant use and dementia, both randomized trials and observational studies have limitations. Most studies investigating this topic are preclinical studies with animal subjects. In randomized clinical trials, the elderly were usually excluded from the eligible patient cohort, so the findings may not be generalizable to the geriatric

population. On the other hand, the existing observational studies suffer from methodologic flaws such as confounding by indication and unmeasured confounders. Additionally, none of the previous studies investigated the causal effects.

Hence, the goal of this study was to evaluate the causal effects of different classes of antidepressant medications on the risk of dementia by conducting a retrospective cohort study using the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS). This study primarily focused on SSRIs, SNRIs, AAs and TCAs. MAOIs were not included due to small numbers who reported taking these drugs.

2.2. Methods

2.2.1. Data Source and Study Population

This study used the NACC's Uniform Data Set (UDS), which is a prospective and longitudinal clinical evaluation database[48]. The data are collected annually from Alzheimer's Disease Centers (ADCs) funded by the National Institute on Aging (NIA)[55]. Since September 2005, all participants in ADC studies have been followed by a standard data collection protocol (i.e., the UDS). The UDS was collected by trained clinicians and clinical practitioners from participants and their co-participants during in-person office visits, home visits and telephone calls. Although the focus of the ADCs is Alzheimer's disease, the UDS also enrolls subjects with a wide range of other related disorders, such as vascular dementia, Lewy body dementia and frontotemporal lobar degeneration. Participants with normal cognition and milder cognitive impairments, like MCI, are also included.

Generally speaking, the UDS subjects are referral-based or volunteer case series[56], thus they are unlikely to be a representative sample of the U.S. population. As of September 2018, among all 38,836 UDS subjects, 35.1% carried a diagnosis of normal cognition, 17.2% were MCI, 4.3% were impaired but not MCI, and 43.4% were diagnosed with any form of dementia. As a comparison, only 8.8% of the U.S. population aged 65 and above was diagnosed with dementia in 2012[57]. In addition, the UDS population consists of slightly higher percentage of females (57.1%), which is consistent with the general population of older adults (56.9%)[58]. However, the percentage of subjects with higher education (72.3% had some college or more) is much higher than the general population of older adults (49.7% of 65 and older had some college or more)[59].

2.2.2. Study Design

A new-user design retrospective cohort study matched on the index visit was conducted using the NACC UDS from September 2005 to September 2018 (see Figure 2.1). Besides the exclusion criteria applied by each ADC, this study further excluded subjects who were:

1) prevalent dementia patients at the index visit;
2) prevalent antidepressant users defined based on reported use at the initial UDS visit;
3) MAOI users or combination users;
4) younger than 65-years-old at the at the initial UDS visit;
5) missing data on any of the covariates in the propensity score model.

In this study, the index visit is defined as the UDS visit when a subject first reported initiation of an antidepressant. The baseline visit is defined as the UDS visit prior to the index visit. The initial visit is the first UDS visit. Due to the sparseness of MAOI users, subjects who reported using this type of antidepressants were excluded from the study. Participants who reported using more than one type of antidepressant were also excluded due to their heterogeneity. Hence, we make comparison among non-users, SSRI users, SNRI users, TCA users and AA users.

2.2.3. Treatment and comparison groups

Among the eligible subjects, those who ever initiated one or more of the treatments prior to a relevant event (dementia, death prior to dementia, or the last UDS visit) were identified. Each subject in the treatment groups was randomly matched with three nonusers who had not started any antidepressant at that same UDS visit to avoid the immortal time bias[60]. Matched non-users may report antidepressant use at a later UDS visit, but they will not contribute follow-up time to the treated cohort. This is similar to an intent-to-treat design.

For example, participant A initiates a certain antidepressant medication at the second UDS visit (Figure 2.2). Three participants (C, G and I) who have not initiated any antidepressant at their second UDS visit will be randomly selected as control subjects. The second UDS visit is the index visit for all four participants. The visit prior to the index-visit, which is first visit in this example, is the baseline visit for these four subjects. Although participant C starts treatment at the fifth visit, this patient will stay in the control group.

2.2.4. Antidepressant Measurement

At each UDS visit, subjects were asked about their antidepressant use within the past two weeks before the current visit. Four classes of antidepressants, SSRIs, SNRIs, TCAs, and AAs were identified based on subjects' self-reported medication use at the index visit. For the purpose of this study, prevalent antidepressant users were removed, and incident antidepressant users and non-users were included.

Prevalent users were defined as active users of any type of antidepressant identified in this study at the initial UDS visit. Incident antidepressant users were defined as new users of any type of antidepressant identified in this study during the follow-up. Non-users were defined as participants who never initiated any antidepressant identified in this study during the follow-up. If a participant reported using two or more classes of antidepressant at one UDS visit, this participant was defined as combination users. As mentioned earlier, combination users were not of the primary interest in this study, five groups are compared: SSRI group, SNRI group, AA group, TCA group and the non-users. Table 2.1 summarizes the antidepressant classification and the generic drug names in each class.

2.2.5. Dementia Status Assessment

Clinicians assessed the cognitive and behavioral status of participants at each UDS visit. Cognitive status is classified into four levels in the UDS: normal cognition, MCI, impaired but not MCI, and dementia. Dementia incidence is defined as the first dementia diagnosis after the index visit. According to the criteria by NACC, a series of

cognitive or behavioral symptoms should be met. Specially, to be diagnosed with dementia, the cognitive impairment should (taken from the UDS coding guide book)[61]:

1) interfere with ability to function as before at work or at usual activities;
2) represent a decline from previous levels of functioning;
3) not be explained by delirium or major psychiatric disorder;
4) include cognitive impairment detected and diagnosed through a combination of history-taking and objective cognitive assessment (bedside or neuropsychological testing).

And, the participant must also show impairment in one or more of the following domains:

1) ability to acquire and remember new information;
2) reasoning and handling of complex tasks, poor judgment;
3) visuospatial abilities;
4) language functions;
5) changes in personality, behavior, or comportment.

2.2.6. Death Assessment

Mortality information is obtained from the NACC Milestone Form[62]. Year and month of death are obtained for subjects who are known to be deceased. Day of death was set to be 15th since this information was not available in the Milestone Form, and we assumed deaths would be distributed randomly and uniformly during the month (thus, the mean day of death for all participants who died in a particular month would be the middle of the month). If a participant died before developing any form of dementia, then this subject is coded to have experience the event of death. Deaths occurring after dementia

diagnosis are not of interest in this study since our focus was on risk of dementia, with death as a competing event.

2.2.7. Administrative Censoring

According to the protocol of the UDS, participants may be censored because participants or co-participants asked to withdraw from the study, or participants could also be withdrawn due to an ADC decision or protocol[62]. For the purpose of this study, if subjects never developed dementia or died, they were right-censored at the last contact. This includes both participants who withdrew and participants still under follow-up.

2.2.8. Baseline Covariates Assessment

A Directed Acyclic Graph (DAG) was constructed via DAGitty.net[63] to identify the minimal sufficient adjustment set based on the hypothesized causal association between antidepressant use and dementia (Figure 2.3). Variables were included in the DAG regardless of their availability in the NACC UDS data. Demographic variables included age, sex, race and education. Lifestyle variables were smoking and alcohol abuse. Comorbidities were traumatic brain injury (TBI), Parkinson's disease, hypertension, type 2 diabetes, high cholesterol, stroke, cardiovascular disease (CVD), depression status, any psychiatric conditions except for depression (i.e. post-traumatic stress disorder, bipolar disorder, schizophrenia or anxiety), standard CDR sum of boxes and cognitive status. History of medication use variables were NSAIDs, opioid medications, and anti-anxiety medications. Genetic information included the ApoE ε4

allele status. Prior antidepressant use was not considered in this graph because prevalent antidepressant users were excluded from the study.

The minimal sufficient adjustment set included the baseline values of age, pain medication use (as proxy for chronic pain), sleep disorders, depression status, GDS score, any other psychiatric conditions except for depression (i.e., post-traumatic stress disorder, bipolar, schizophrenia, anxiety, obsessive-compulsive disorder or developmental neuropsychiatric disorder), standard CDR sum of boxes and cognitive status.

2.2.9. Statistical Analysis

2.2.9.1. Descriptive analysis

Subject characteristics at baseline stratified by the treatment groups were summarized for the original cohort and the pseudo-cohort (the pseudo-cohort is defined and described below). Means and standard deviations were reported for normally-distributed continuous variables. Median and interquartile range were reported for non-normally-distributed variables. Frequencies and percentages were reported for categorical variables.

2.2.9.2. Main analysis

Kaplan-Meier curves by treatment groups were plotted to visualize the distribution of dementia-free-survival-times across the five groups. Log-Rank tests between each treatment group and the control group were performed to quantitively compare the median dementia-free-times.

Cox Proportional Hazard Regression with IPW was performed to evaluate the effects of different antidepressant classes on the risk of dementia. To perform this analysis, it is necessary to 1) build propensity score models to obtain the weights for balancing the subject baseline characteristics; 2) apply weights to the original cohort to construct a "weighted and balanced" pseudo-cohort; 3) evaluate the balance of the pseudo-cohort; and 4) construct a weighted Cox Proportional Hazards regression with antidepressant treatment status as the only predictor in the model. The model in step 4 is called a marginal structural model and estimates the marginal causal effects of antidepressants on the risk of developing dementia. Standardized Mean Differences (SMDs) between each treatment group and the control group were calculated to assess the effectiveness of the inverse probability weighting in balancing the baseline characteristics of the treated and untreated groups in the pseudo-cohort.

Two propensity score models were built to obtain two sets of weights respectively: weights for balancing the prognostic factors of receiving different classes of antidepressant (i.e. inverse probability of treatment weights), and the weights for accounting for censoring (i.e. inverse probability of censoring weights).

The propensity score model of treatment predicted a participant's probability of receiving a particular treatment given the observed participant factors via a multinomial logistic regression with the five treatment groups as the outcome. The model produces probabilities of receiving each of the five treatments, which sum to 1.00, for each participant. Participants are then weighted by the inverse of the predicted probability of the treatment that they actually received. Stabilized weights were calculated by multiplying the inverse of the predicted probabilities of receiving the observed treatment

by the observed marginal probabilities of receiving this treatment[64]. Selection of covariates included was based on the minimal sufficient adjustment set from the DAG (Figure 2.3), which were the baseline values of age, chronic pain, sleep disorders, depression status, GDS score, any other psychiatric conditions except for depression, and cognitive status. Chronic pain is not directly measured in the UDS, thus NSAIDs or opioid medication use was used as a surrogate for chronic pain. Additionally, sleep disorder variables were not included in the model due to the fact of heavy missingness (sleep disorder data have been collected in the UDS only since March 2015).

The propensity score model of censoring predicts the probability of being censored given the observed covariate values at baseline via a binary logistic regression with censoring as the outcome. Covariates adjusted in this model are baseline characteristics that we believed to be associated with being censored. Specifically, sex, age, years of education, race, smoking, alcohol abuse, history of TBI, Parkinson's disease, hypertension, diabetes, high cholesterol, stroke, cardiovascular disease, chronic pain, depression status, other psychiatric conditions and cognitive status were included in the model. Stabilized weights were calculated by multiplying the inverse of the predicted probabilities of being censored given the observed covariates values by the observed marginal probabilities of being censored[64].

The joint weights for balancing the overall subject baseline characteristic distributions are computed by multiplying the stabilized weights for treatment and the stabilized weights for censoring[65]. The joint weights are applied to the original cohort to obtain a pseudo-cohort, or "weighted cohort". In the weighted cohort, the overall measured baseline characteristic distributions are balanced among the treatment groups.

Such balance of measured baseline characteristics mimics a randomized clinical trial, in which the probabilities of being assigned to any treatment arm are independent of confounding variables, and the probabilities of being censored are independent as well. The use of both weights jointly adjusts for both confounding at baseline and selection bias during follow-up. Standardized mean differences between each treatment group and the control group were calculated to assess the effectiveness of weighting.

A weighted Cox Proportional Hazards regression with antidepressant treatment status as the only predictor in the model was performed to estimate the marginal effects of antidepressants on the risk of developing dementia. The proportional hazards assumption was checked by incorporating an interaction term of treatment by time in the model.

2.2.9.3. Sensitivity Analyses

Three sensitivity analyses were conducted to assess the robustness of the main analysis results. Sensitivity Analysis One used a restricted cohort with participants who had not reported a diagnosis of depression or any other psychiatric conditions at the baseline visit. All other analysis procedures remained the same as the main analysis. The aim of Sensitivity Analysis One was to determine if the estimates in the main analysis were impacted by confounding by indication, where the observed effect of the medications is actually due to the pre-existing psychiatric conditions.

Sensitivity Analysis Two further includes ApoE ε4 status in the IPW model in addition to the covariates adjusted in the IPW model in the main analysis. All other analysis procedures remained the same as the main analysis. There is no evidence that

ApoE ε4 status is related to antidepressant use. However, ApoE ε4 carriers are at greater risk of developing Alzheimer's disease compared with others[66], and it has been hypothesized that depression may occur during the preclinical phase of the disease[67]. The purpose of the Sensitivity Analysis Two was to determine if ApoE ε4 status would influence the estimates even though it was not hypothesized to be a confounder in the pathway between antidepressant use and dementia.

Sensitivity Analysis Three used time-varying treatment instead of the fixed treatment at the index visit. Changes between any treatment groups, including change from one class to another, users to non-users or vice versa, were allowed. Participants' baseline characteristics were balanced using the IPW. A Cox Proportional Hazards regression with treatment as the time-varying covariate in the model was performed. The aim of Sensitivity Analysis Three was to determine if the estimates in the main analysis were impacted by the potential treatment regimen changes in later UDS visits.

2.3. Results

2.3.1. Descriptive Summaries

Participant characteristics at study baseline (i.e., the visit prior to the index visit) are summarized in Table 2.2. Briefly, approximately 75% of the included subjects were antidepressant-naïve, 14.4% of the subjects initiated SSRI use, 2.3% of the subjects initiated SNRI use, 5.4% of the subjects initiated AA use, and 2.9% of the subjects initiated TCA use. In total 645 out of 4302 participants (15.0%) were diagnosed with incident dementia during follow-up. Treatment groups had higher proportions of participants who developed dementia (26.7%, 18.2%, 19.2% and 16.8% for SSRIs,

SNRIs, AAs and TCAs respectively) compared to the control group (12.3%). SSRI, SNRI and AA users were estimated to have shorter median dementia-free-survival-times (2.7, 2.2, and 3.0 years for SSRIs, SNRIs, and AAs respectively) compared to the non-user group (3.1 years). However, the diagnoses may not occur on the visit date thus the dementia-free-survival times may be overestimated.

Mean baseline ages across the five groups were similar; the SNRI group had the lowest mean baseline age and the AA group had the highest (Table 2.2). Regarding the use of pain medications, SNRI users, AA users, and TCA users had higher proportions of subjects who reported using NSAIDs or opioid medications compared to controls and SSRI users. Psychiatric disorders, including depression and any other psychiatric conditions, were in general more common among the antidepressant users (SSRIs, SNRIs, AAs, and TCAs) than among the controls. Antidepressant users also tended to have higher burden of depressive symptoms compared to the controls, based on the Geriatric Depression Scale (Table 2.2). Even though there is not much difference regarding the standard CDR sum of boxed across the groups, the control group had more participants with normal cognition at baseline, while the antidepressant groups had more participants with MCI at baseline. Hence, the distributions of the risk factors for dementia are not balanced across groups. In other words, the treatment groups and control group are not exchangeable.

Table 2.3 summarizes the baseline characteristics for the weighted cohort (pseudo-cohort). In the weighted cohort, the risk factors for dementia at baseline were distributed with good balance across the five groups in general. The SMDs of the baseline risk factor values between each treatment group and the control group in the

observed cohort are larger than 0.1 in general, indicating that the baseline risk factor distributions are not comparable between each antidepressant group and the control group. In the weighted cohort, the SMDs between each antidepressant group and the control group are significantly reduced, suggesting balance across groups (Figure 2.4).

2.3.2. Main Analysis

Kaplan-Meier curves (Figure 2.5) and the Log-Rank test results showed that the users of any antidepressant had significantly shorter median dementia-free-survival-times compared to the control group (P-values<.0001). Among the antidepressant classes, SSRI users had significantly shorter dementia-free-times compared to other antidepressant users (P-values <.0001). There were no significant pair-wise differences among SNRI users, AA users, and TCA users.

A weighted Cox Proportional Hazards regression model with antidepressant treatment as the only predictor in the model was performed. Subjects who reported using SSRIs, SNRIs, AAs, and TCAs at the index visit were estimated to have 2.04 (1.69-2.48), 2.10 (1.33, 3.31), 1.46 (1.05, 2.03) and 1.58 (1.04, 2.41) times the hazard of developing dementia compared to subjects who did not report using any antidepressants at the index visit, respectively. In other words, antidepressant users progressed to dementia more quickly compared to the non-users. All estimated effects were significant at the 0.05 significance level. There is no evidence that the proportional hazards assumption was violated (P-value=0.5387).

2.3.3. Sensitivity Analyses

The point estimates for hazard ratio obtained from Sensitivity Analysis One, where only participants who did not report a psychiatric diagnosis were included, remained consistent with the main analysis in general, indicating that the estimates were not sensitive to confounding by indication. In Sensitivity Analysis Two, where ApoE ε4 status was included in the propensity score model, the point estimates of a hazard ratios remain consistent with the estimates in the Main Analysis. However, the estimated confidence intervals in Sensitivity Analysis One and Sensitivity Analysis Two for AA users and TCA users contains the null hazard ratio one. This was likely due at least in part to the reduced sample size, because ApoE ε4 genotyping was unavailable for 7.2% of participants. Sensitivity Analysis Three, which allowed treatment status to vary over time, also generated consistent estimated hazard ratios compared to estimates in the Main Analysis.

2.4. Discussion

In this study, we found that all antidepressant classes investigated increased the hazard for dementia. SNRIs increase the levels of serotonin and norepinephrine in brain, and both chemicals have been reported to enhance cognitive functions[68,69], but in this analysis SNRI use was associated with the shortest dementia-free-time. A possible explanation is that SNRIs may increase the risk of dementia via hypertension as a mediator. It is known that SNRIs may increase users' blood pressure[64,70], and hypertension has been reported as a risk factor for vascular dementia and Alzheimer's dementia[71]. In this study, SNRI users had a higher proportion of participants reporting

hypertension at baseline (64.7% for SNRI users versus 61.1% for SSRI users, 62.0% for AA users, 59.4% for TCA users and 58.1% for controls). Hence, the SNRI users may have higher risk of dementia at least in part because of the increased high blood pressure. Alternatively, if SNRI treatment is related to the presence of preclinical neurodegenerative disease (i.e., it is a result of reverse causality), this could explain the association.

The underlying biological mechanism for increased dementia risk in SSRI users remains unclear[22]. A possible explanation is that there might be a pathway between SSRIs and dementia through zinc. An animal study has found upregulation of the GPR39 Zn^{2+}-sensing receptor protein level after SSRI treatment[72]. Imbalance in zinc levels may lead to neurofibrillary tangles, which is believed to be a marker of Alzheimer's disease and cognitive impairment[73], but further research on human subjects is still needed in answering this question. Again, if SSRI treatment is related to the presence of preclinical neurodegenerative disease, this could also explain the association.

In clinical practice, AAs are often prescribed for treating other health conditions besides depression. For example, trazodone is the second most commonly prescribed medication for treating insomnia[74], and insomnia is a risk factor for dementia[75]. The link between AA use and dementia may be through unrecognized and unmeasured confounders like insomnia. TCAs are usually not prescribed as the first-line treatment for the elderly because TCAs may cause more side effects compared to other agents[76]. These side effects include blurred vision and drop in blood pressure when moving from sitting to standing[77], which may be linked with dementia via the risk of falls. As with SNRIs and

SSRIs, if treatment is related to the presence of preclinical neurodegenerative disease, this could explain the association.

There are several strengths of this study. First, successful IPW in this study reduces selection bias at baseline by creating a balanced pseudo-cohort, in which the probability of receiving a certain antidepressant treatment is independent of the observed baseline prognostic factors. Hence, the average causal effects of each antidepressant class on the risk of dementia were estimated in this study. While we do not assume that all the conditions for causal inference based on observational data were met fully in this study, we think it is valuable to carefully consider the hypothesized causal model and to be transparent about the assumptions we made. Second, all potential confounders would be included in the propensity score model in a conventional approach, however this approach has been proved inadequate[32,33]. In this study, a DAG was built to identify the minimal sufficient set for confounder adjustment. The DAG reduces the number of parametric assumptions needed for this study compared to the number of parametric assumptions needed in a conventional approach.

This study has some limitations. First, we did not control for all sources of confounding. For example, we were not able to control well for confounding by depression severity. Also, due to the inconsistent data collection protocols over time, some important variables, like those documenting sleep disorders, were only collected for UDS version 3, which was implemented in 2015, and are not available for UDS visits prior to this new implementation. This leads to missingness on some major potential confounders, such as sleep apnea history, REM sleep behavior disorder history, and insomnia history. Furthermore, participants' treatment groups are fixed at the index visit,

regardless of any treatment regimen change in later visits. Change of antidepressant treatment may indicate depression progression or medication resistance, but these issues were largely ignored in this study. However, the sensitivity analysis that allowed participants to change medications did not provide evidence that our main results were due these factors. Another limitation is that the measurement of treatment is not ideal. For example misclassification of treatment is possible given the long gap between two visits; also there is no information about dosage or length of treatment. Drug-drug interaction was not investigated. It is common that the elderly may simultaneously take multiple medications given the complex health conditions associated with aging, but the possibility of drug-drug interaction was not considered for this study. We also cannot exclude the possibility of reverse causality[78], where preclinical neurodegenerative disease causes depression, which causes antidepressant initiation, which induces the association between antidepressant use and dementia. Studies with decades of follow-up, where incident cases that arise in the first pre-determined number of years of treatment are excluded, are needed to test the reverse causality hypothesis[79]. Finally, we could not examine the effects of individual antidepressant medications or conduct proper comparative effective research due to sample size limitations.

2.5. Conclusion

In this study, Cox Proportional Hazard Regression with Inverse Probability Weighting was performed to evaluate the effects of different antidepressant classes on the risk of dementia. Significant causal effects of SSRIs, SNRIs, AAs and TCAs on the risk of dementia were observed at the 0.05 significance level. In general, the estimates were

not sensitive to confounding by indication of psychiatric disorders, genetic risk due to ApoE ε4, or treatment regime switches in later visits.

All medications carry some risk of side effects that must be weighed against the therapeutic benefit of the medications. For depressed elderly, antidepressant therapies are important for maintaining quality of life. The question of whether their use causes an increased risk of dementia causing diseases remains open, and the answer is important. However, it is clearer is that the use of these antidepressant classes appears to hasten the onset of dementia diagnosis in this population.

Table 2.1. Antidepressant Classifications and Generic Drug Names

Classification	Generic Drug Name
SSRI[1]	fluoxetine, paroxetine, sertraline, citalopram, escitalopram, vilazodone
SNRI[2]	duloxetine, venlafaxine, desvenlafaxine, levomilnacipran
AA[3]	trazadone, mirtazapine, vortioxetine, bupropion, nefazodone
TCA[4]	imipramine, nortriptyline, amitriptyline, doxepin, desipramine, amoxapine, protriptyline, trimipramine

[1]Selective serotonin reuptake inhibitors
[2]Serotonin and norepinephrine reuptake inhibitors
[3]Atypical antidepressants
[4]Tri-cyclic antidepressants

Table 2.2. Subject Characteristics at Baseline for the Observed Cohort

	None	SSRI[1]	SNRI[2]	AA[3]	TCA[4]
N	3225 (75.0)	619 (14.4)	99 (2.3)	234 (5.4)	125 (2.9)
Age (year)	77.5 ± 7.3	76.1 ± 7.2	74.8 ± 6.9	77.1 ± 7.9	76.7 ± 8.2
Pain meds[5]	1430 (44.3)	279 (45.5)	51 (51.5)	123 (52.6)	68 (54.4)
Depression	410 (12.7)	274 (44.3)	51 (51.5)	90 (38.6)	35 (28.2)
GDS[6]	0 (0, 1)	1 (0, 3)	2 (0, 4)	1 (0, 2)	1 (0, 2)
Psychiatric[7]	110 (3.4)	60 (9.7)	6 (6.1)	19 (8.1)	4 (3.2)
CDR[8]	0 (0, 0.5)	0.5 (0, 1)	0 (0, 1)	0 (0, 0.5)	0 (0.5)
Cognition					
Normal	2442 (75.7)	336 (54.3)	63 (63.6)	152 (65.0)	91 (72.8)
Impaired[9]	148 (4.6)	67 (10.8)	10 (10.1)	11 (4.7)	3 (2.4)
MCI[10]	635 (19.7)	216 (34.9)	26 (26.3)	71 (30.3)	31 (24.8)
ApoE ε4 +	871 (29.0)	189 (33.4)	32 (37.2)	71 (31.6)	31 (27.2)
Dementia incidence	396 (12.3)	165 (26.7)	18 (18.2)	45 (19.2)	21 (16.8)
Time to dementia (year)	3.1 (1.9, 5.5)	2.7 (1.2, 4.9)	2.2 (1.2, 4.8)	3.0 (1.6, 4.8)	3.3 (1.4, 5.2)

Note: Mean ± S.D. are reported for normally-distributed continuous variables. Median (Q1, Q3) are reported for non-normally-distributed variables. Frequency (%) are reported for categorical variables.

[1]Selective serotonin reuptake inhibitors
[2]Serotonin and norepinephrine reuptake inhibitors
[3]Atypical antidepressants
[4]Tri-cyclic antidepressants
[5]NSAIDs or opioid medications
[6]Total Geriatric Depression Scale Score
[7]Any other psychiatric conditions except for depression, including post-traumatic stress disorder, bipolar, schizophrenia, anxiety, obsessive-compulsive disorder or developmental neuropsychiatric disorder
[8]CDR sum of boxes
[9]Impaired but not MCI
[10]Mild Cognitive Impairment

Table 2.3. Subject Characteristics at Baseline for the Weighted Cohort

	None	SSRI[1]	SNRI[2]	AA[3]	TCA[4]
N	3200	651	100	240	127
Age (year)	77.4 ± 7.3	77.6 ± 7.6	76.9 ± 7.1	77.6 ± 7.8	77.6 ± 8.1
Pain meds[5]	1479 (45.9)	305 (47.7)	53 (51.6)	108 (44.8)	55 (43.3)
Depression	657 (20.5)	146 (22.5)	24 (24.3)	54 (22.5)	24 (19.2)
GDS[6]	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)
Psychiatric[7]	162 (5.0)	40 (6.2)	5 (5.1)	15 (6.0)	4 (3.2)
CDR[8]	0 (0, 0.5)	0 (0, 0.5)	0 (0, 0.5)	0 (0, 0.5)	0 (0, 0.5)
Cognition					
Normal	2254 (70.4)	464 (71.3)	74 (73.6)	167 (69.4)	94 (73.7)
Impaired[9]	188 (5.9)	39 (6.0)	6 (6.3)	14 (5.7)	6 (4.6)
MCI[10]	758 (23.7)	148 (22.7)	20 (20.1)	60 (24.9)	28 (21.7)

Note: Mean ± S.D. are reported for normally-distributed continuous variables. Median (Q1, Q3) are reported for non-normally-distributed variables. Frequency (%) are reported for categorical variables.

[1]Selective serotonin reuptake inhibitors
[2]Serotonin and norepinephrine reuptake inhibitors
[3]Atypical antidepressants
[4]Tri-cyclic antidepressants
[5]NSAIDs or opioid medications
[6]Total Geriatric Depression Scale Score
[7]Any psychiatric conditions except for depression, including post-traumatic stress disorder, bipolar, schizophrenia, anxiety, obsessive-compulsive disorder or developmental neuropsychiatric disorder
[8]Standard CDR sum of boxes
[9]Impaired but not MCI
[10]Mild Cognitive Impairment

Table 2.4. Hazard Ratios (95% CIs) for Main Analysis and Sensitivity Analyses

	Main Analysis	Sensitivity Analysis One[1]	Sensitivity Analysis Two[2]	Sensitivity Analysis Three[3]
SSRI[4]	2.04 (1.69, 2.48)	1.93 (1.49, 2.51)	1.82 (1.48, 2.23)	2.78 (2.26, 3.42)
SNRI[5]	2.10 (1.33, 3.31)	2.56 (1.37, 4.75)	2.24 (1.39, 3.60)	3.01 (1.95, 4.64)
AA[6]	1.46 (1.05, 2.03)	1.42 (0.89, 2.25)	1.36 (0.95, 1.93)	1.80 (1.23, 2.64)
TCA[7]	1.58 (1.04, 2.41)	1.53 (0.92, 2.54)	1.12 (0.68, 1.86)	1.67 (0.90, 3.12)

[1]Restricted analysis on participants without any psychiatric disorders
[2]Restricted analysis on participants with ApoE ε4 measurement and ApoE ε4 status was adjusted in the propensity score model
[3]Analysis allows for time-varying treatment
[4]Selective serotonin reuptake inhibitors
[5]Serotonin and norepinephrine reuptake inhibitors
[6]Atypical antidepressants
[7]Tri-cyclic antidepressants

Figure 2.1. Study Cohort Derivation Flowchart

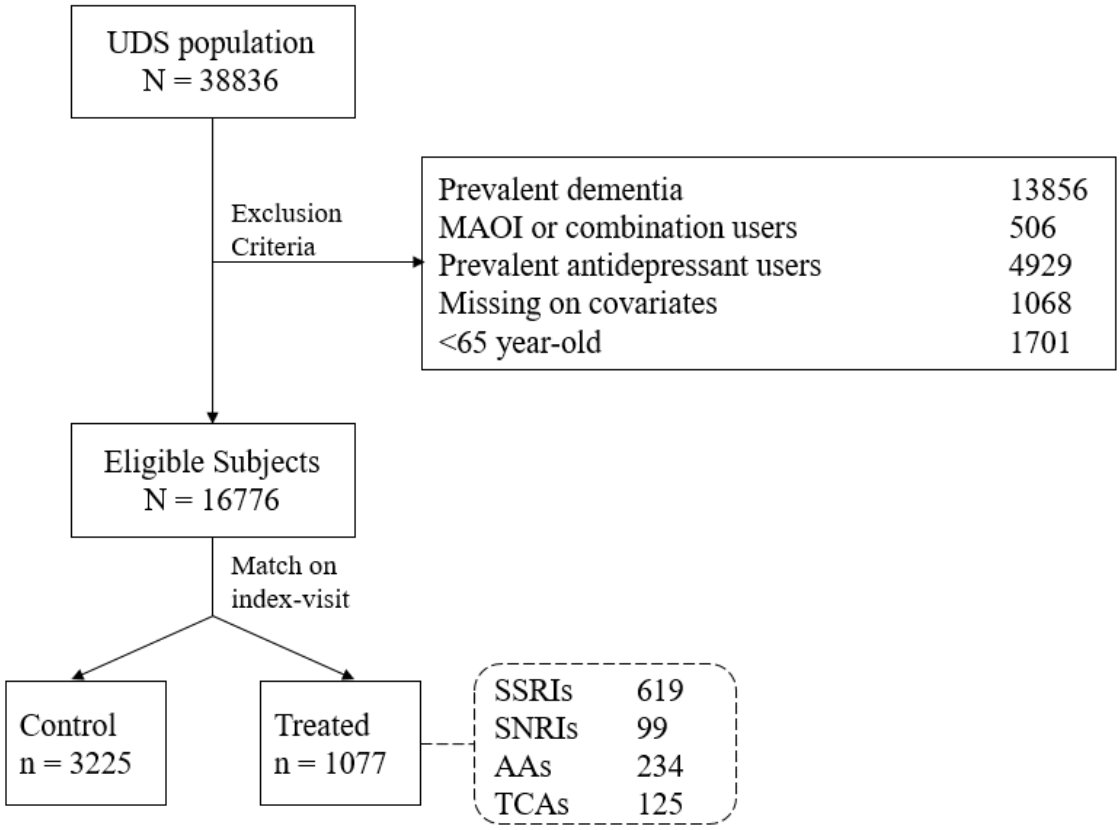
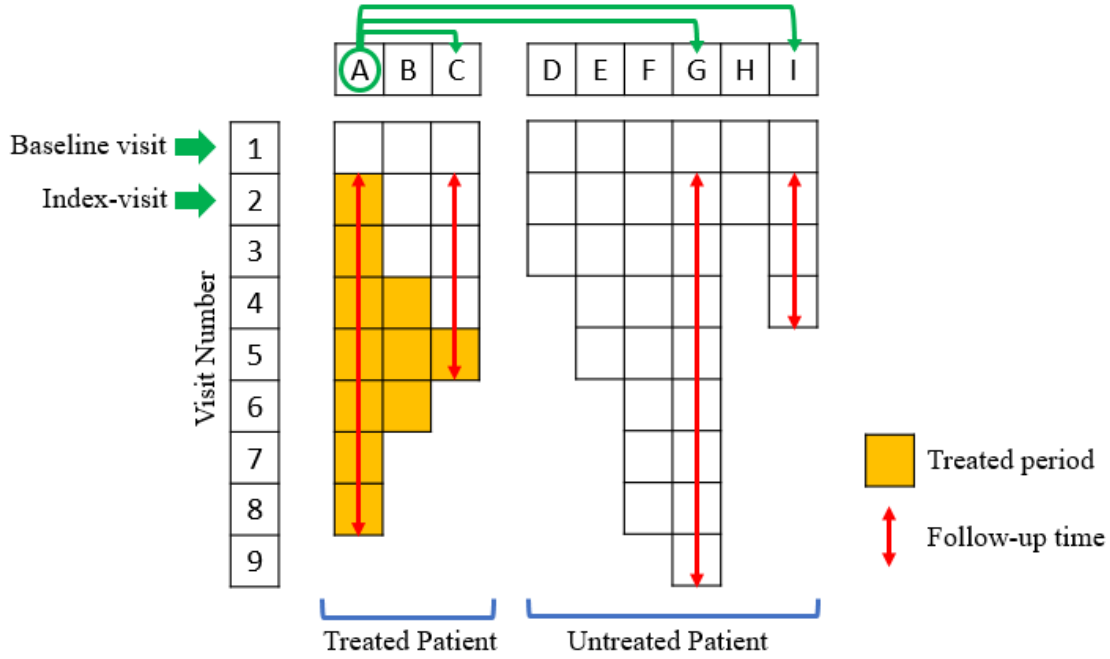


Figure 2.2. Illustration of Matching Process



Note: This figure is for illustrative purpose only. Participant information used for this graph is not true information from the data.

Figure 2.3. Directed Acyclic Graph for Assessing the Minimum Sufficient Adjustment Set

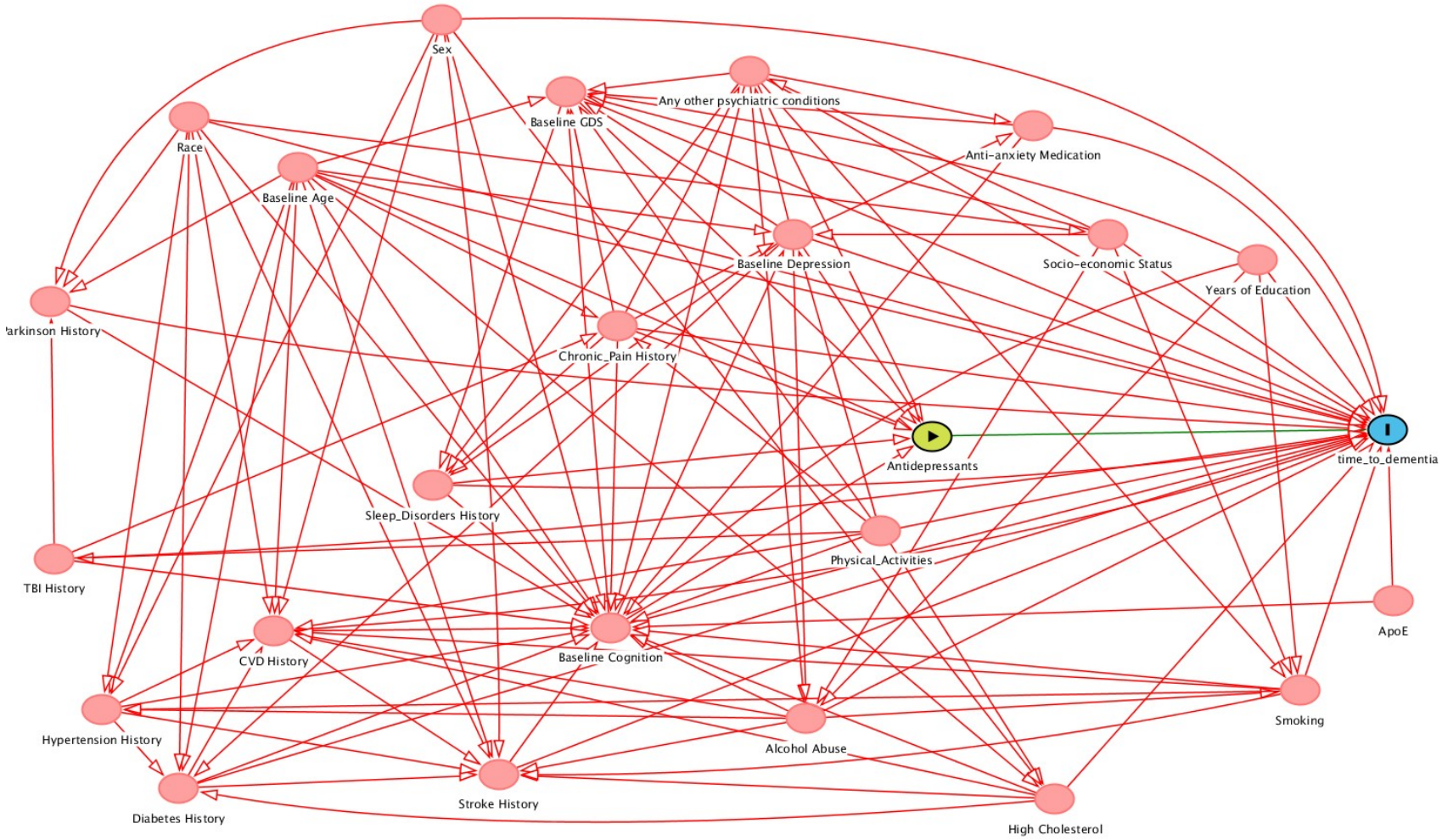


Figure 2.4. Standardized Mean Difference Comparisons

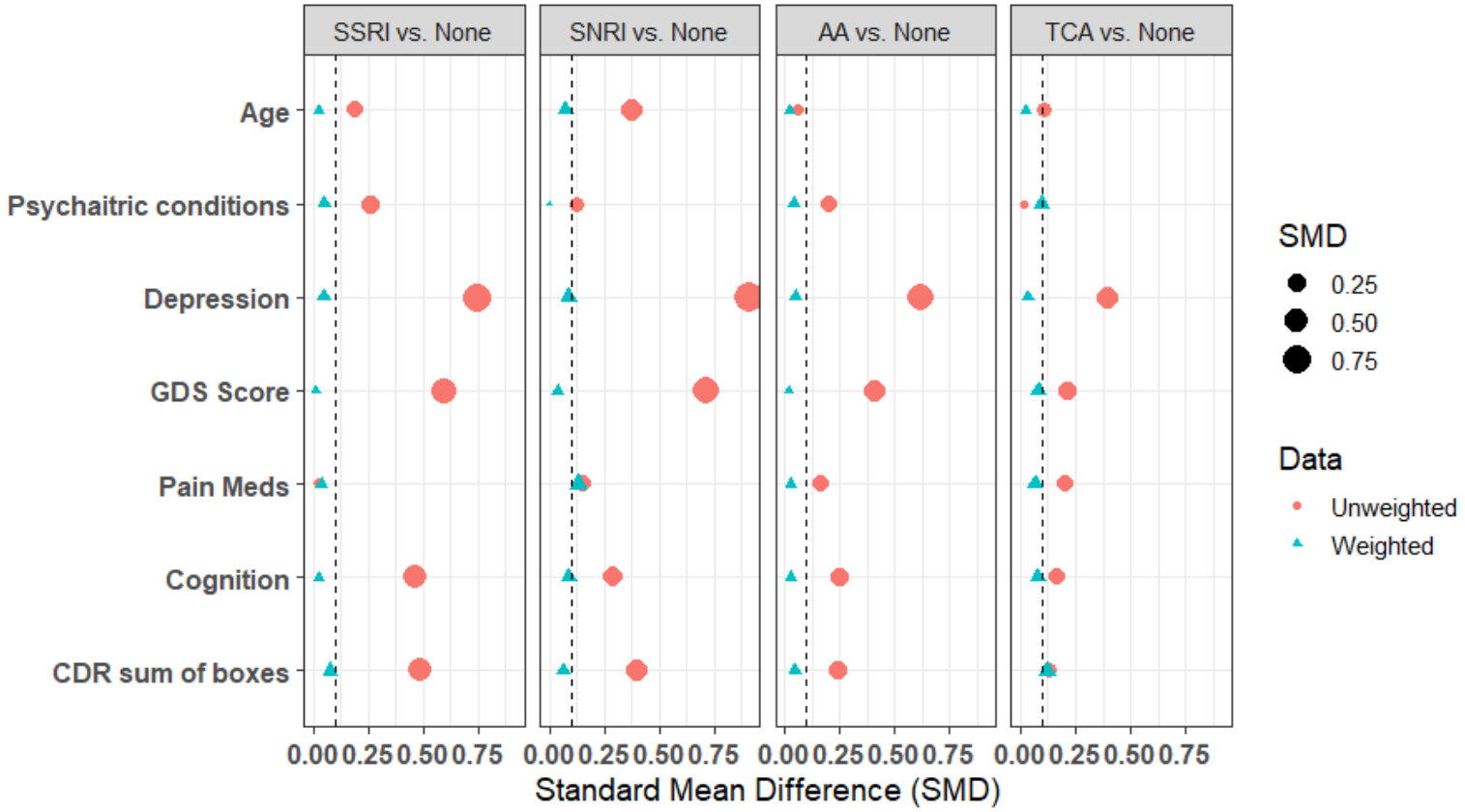
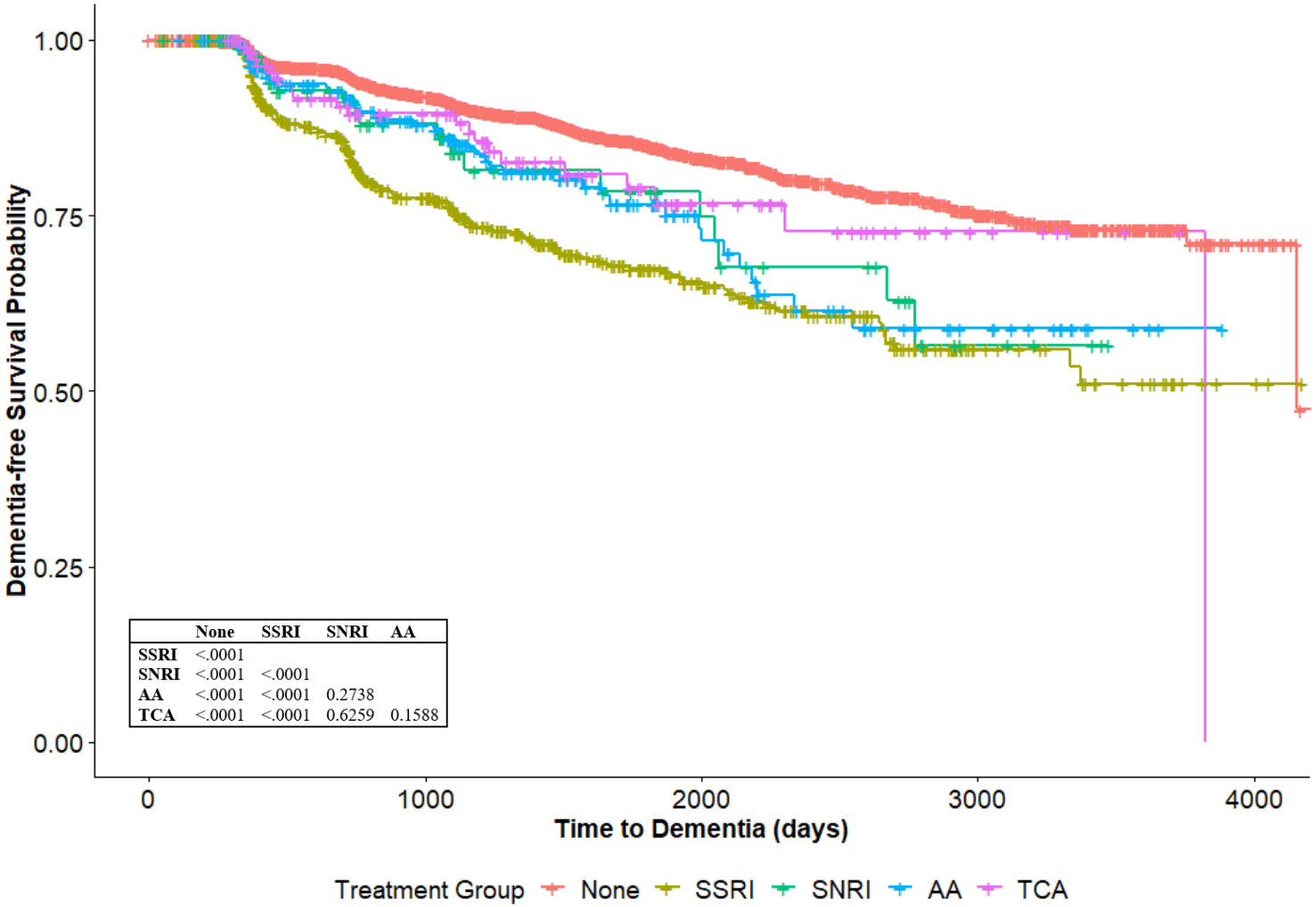


Figure 2.5. Kaplan-Meier Curves by Treatment Groups and Log-rank Tests between Treatment Groups for the Original (unweighted) Cohort



CHAPTER THREE. THE EFFECTS OF UNMEASURED SLEEP DISORDERS ON THE RELATIONSHIP BETWEEN ANTIDEPRESSANT USE AND THE RISK OF DEMENTIA

3.1. Introduction

In epidemiologic studies, causal effects of an exposure on an outcome are of interest. Causation can be inferred in an ideal randomized trial, because randomization will ensure the exchangeability between the exposed group and the unexposed group[80]. However, since randomization is often not feasible, we are left with observational data where the exposed group and the unexposed group are not always comparable to each other[34]. It is common in observational studies that confounding is controlled by statistical methods, but the potential uncontrolled confounding may still lead to distorted estimation of the association between exposure and outcome. It is generally expected that exchangeability and perfect adjustment of all confounders will not be true in observational studies.

In Chapter Two, Inverse Probability Weighting methods were used to assess the average causal effects of antidepressants on the risk of dementia using National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). A pseudo-cohort, in which the prognostic factors for receiving a certain type of treatment were balanced across groups, was constructed under the assumption that there was no unmeasured confounding given the observed data. The impacts of antidepressants on the risk of dementia were evaluated using the pseudo-cohort so that the causal effects could be inferred. Nevertheless, the assumption that there are no unmeasured confounders may not be true.

There are several reasons why the assumption of no unmeasured confounding may not be true. First, some hypothetical confounders for the association between antidepressant use and dementia, including socio-economic status and physical activities, are not measured in the UDS. Second, even for hypothetical confounders measured in the UDS, some of them are not usable for the purpose of this study. For example, information about sleep apnea, rapid-eye-movement behavior disorder (RBD), and insomnia is only collected for the UDS version 3, which was implemented in March 2015. UDS visits prior to the implementation of the UDS version 3 (September 2005-February 2015) did not collect this information. In other words, these variables suffer from heavy missingness.

Based on our hypothesized causal model, an ideal observational study that evaluates the effects of antidepressants on the risk of dementia would include measurements for age, sex, race, education, socio-economic status, smoking, alcohol abuse, physical activities, traumatic brain injury (TBI), Parkinson's disease, hypertension, type 2 diabetes, high cholesterol, stroke, cardiovascular disease (CVD), chronic pain, sleep disorders, depression status, any other psychiatric conditions except for depression (for example anxiety etc.), cognitive status, anti-anxiety medication use, and ApoE ε4 allele status[81,82] (see Figure 2.3). As mentioned previously, socio-economic status and physical activities are not measured in the UDS, and sleep disorder variables suffer from heavy missingness. Based on Figure 2.3, the minimal sufficient adjustment set includes baseline age, chronic pain, sleep disorders, depression status, Geriatric Depression Scale (GDS) score, any other psychiatric conditions except for depression (i.e. post-traumatic stress disorder, bipolar, schizophrenia, anxiety, obsessive-compulsive disorder or

developmental neuropsychiatric disorder), standard CDR sum of boxed, and cognition. Unfortunately, sleep disorders could not be included in the analysis.

Failing to adjust for sleep disorders in the analysis may lead to inaccurate effect estimates. For example, a series of studies have investigated the impact of sleep apnea on cognition, and it is believed that sleep apnea is associated with cognitive dysfunctions[83-85]. Similarly, studies suggest that Rapid Eye Movement Behavior Disorder (RBD) and insomnia are associated with impaired cognition[75,86-88]. On the other hand, sleep disorders are associated with antidepressant use. For example, SSRIs may cause insomnia[89], and trazodone, which is a type of atypical antidepressant, is often used for treating insomnia[90].

In this study, the effects of sleep disorders as unmeasured confounders for the association between antidepressant use and the risk of dementia were investigated. The average causal effects of antidepressants on the risk of dementia adjusted for both measured and unmeasured confounders were assessed.

3.2. Methods

In Chapter Two, the effects of different classes of antidepressant were estimated assuming we controlled for all potential confounders. This assumption may not be valid due to the omission of sleep disorders. Hence, in this Chapter, 1) a bias factor formula for two binary unmeasured confounders is derived; 2) Monte Carlo Sampling is implemented to estimate the distribution of the bias factor for each class of antidepressant; 3) the effects of antidepressants on the risk of dementia are adjusted for both measured and unmeasured confounders are estimated. Table 3.1 summarizes the confounder adjustments status in this research.

3.2.1. Formula of Bias Factor

For the purposes of this study, we limit our discussion to two binary unmeasured confounders. Let X be the indicator for use of a certain class of antidepressant, $\boldsymbol{Z}$ be a vector of controlled covariate values at baseline, U_1 be the indicator for uncontrolled confounder 1, and U_2 be the indicator for uncontrolled confounder 2. Let HR_{obs} be the estimated observed hazard ratio for a certain class of antidepressant that is adjusted for the effects of the covariates in $\mathbf{Z}$, but does not adjust for the effects of $\boldsymbol{U}$. HR_{obs} can be written as:

$$HR_{obs} = \frac{\lambda_0(t) \cdot \exp(\beta(X = 1) + \gamma \boldsymbol{Z})}{\lambda_0(t) \cdot \exp(\beta(X = 0) + \gamma \boldsymbol{Z})}$$

$$= \exp(\beta)$$

Let HR_{adj} be the hypothetical hazard ratio for a certain class of antidepressant that adjusted for the effects of both $\boldsymbol{Z}$ and $\boldsymbol{U}$. HR_{adj} is the target parameter of interest in this study, and it can be written as:

$$HR_{adj} = \frac{\lambda_0(t) \cdot \exp(\beta^*(X = 1) + \gamma^* \boldsymbol{Z} + \omega \boldsymbol{U}))}{\lambda_0(t) \cdot \exp(\beta^*(X = 0) + \gamma^* \boldsymbol{Z} + \omega \boldsymbol{U}))}$$

$$= \exp(\beta^*)$$

Let P_{X,U_1,U_2} denote the proportion of subjects for the specific U_1-U_2 stratum in group X=x. For example, $P_{1,1,0}$ is the proportion of subjects who reported using a certain class of antidepressant X=1 and have condition U_1but not U_2.

The change in the hazard for the control group due to U_1 and U_2, denoted as HR^*_{ctrl}, is a weighted average of the hazard ratios for strata of $(U_1 = 0, U_2 = 0)$, $(U_1 =$

$1, U_2 = 0)$, $(U_1 = 0, U_2 = 1)$ and $(U_1 = 1, U_2 = 1)$ in the control group using $P_{0,0,0}$, $P_{0,1,0}$, $P_{0,0,1}$, $P_{0,1,1}$ as weights. HR^*_{ctrl} can be written as:

$$HR^*_{ctrl} = \sum_{U_1} \sum_{U_2} \exp(\omega_1 U_1 + \omega_2 U_2) P_{0,U_1,U_2}$$

$$= P_{0,0,0} + \exp(\omega_1) P_{0,1,0} + \exp(\omega_2) P_{0,0,1} + \exp(\omega_1 + \omega_2) P_{0,1,1}$$

Similarly, the change in the hazard for a certain class of antidepressant due to U_1 and U_2, denoted as HR^*_{trt}, can be written as:

$$HR^*_{trt} = \sum_{U_1} \sum_{U_2} \exp(\omega_1 U_1 + \omega_2 U_2) P_{1,U_1,U_2}$$

$$= P_{1,0,0} + \exp(\omega_1) P_{1,1,0} + \exp(\omega_2) P_{1,0,1} + \exp(\omega_1 + \omega_2) P_{1,1,1}$$

where $\sum_U$ means sum over all values of U.

Any difference between HR^*_{ctrl} and HR^*_{trt} can only be due to the differences in the distributions of U_1 and U_2 between the treatment group and the control group. Therefore, the change in hazard due to differences in U_1 and U_2 between the treatment group and the control group can be written as:

$$Bias = \frac{HR^*_{trt}}{HR^*_{ctrl}} = \frac{P_{1,0,0} + \exp(\omega_1) P_{1,1,0} + \exp(\omega_2) P_{1,0,1} + \exp(\omega_1 + \omega_2) P_{1,1,1}}{P_{0,0,0} + \exp(\omega_1) P_{0,1,0} + \exp(\omega_2) P_{0,0,1} + \exp(\omega_1 + \omega_2) P_{0,1,1}}$$

(Formula 1)

Hence, the observed HR adjusted for U_1 and U_2, i.e. HR_{adj}, can be estimated by dividing the Hazard Ratio that did not adjust for U_1 and U_2, i.e. HR_{obs}, by the above derived bias factor:

$$HR_{adj} = \frac{HR_{obs}}{Bias}$$

(Formula 2)

3.2.2. Monte Carlo Sampling

In this study, four bias factors need to be estimated: SSRI users relative to controls, SNRI users relative to controls, AA users relative to controls, and TCA users relative to controls. Monte Carlo Sampling was performed to estimate the distribution of each bias factor.

The prior distribution of the HR for sleep apnea was obtained from a large population-based retrospective matched-control cohort study using the Longitudinal Health Insurance Database 2005 in Taiwan[91]. The study cohort comprised 1414 subjects with sleep apnea and 7070 subjects without sleep apnea who were matched with the sleep apnea subjects on sex, age and index-year. A Cox Proportional Hazards regression model was performed to estimate the 5-year dementia-free survival rates after adjusting for potential confounders. The investigators concluded that subjects with sleep apnea have 1.70 (95% CI: 1.26-2.31) times the hazard of developing dementia within 5 years of diagnosis compared to subjects without sleep apnea after adjusting for potential confounders.

The prior distribution of the HR for RBD on the risk of dementia was obtained from a population-based cohort study investigating the impacts of RBD on the risk of MCI, dementia or Parkinson's disease[87]. Subjects were randomly selected from the 70-89 years old residents of Olmsted County, Minnesota, USA to participant in the Mayo Clinic Study of Aging. The study cohort consists of 44 subjects with probable RBD and 607 subjects without probable RBD. A Cox Proportional Hazards regression model was performed to estimate the adjusted hazard ratio and the corresponding 95% confidence intervals after adjusting for age, sex, education and medical comorbidities. The subjects

were followed prospectively for a median of 3.8 years. Subjects with probable RBD had 2.2 (95% CI: 1.3-3.9) times the hazard of MCI/PD (no subject developed dementia by the end of the study) compared to subjects without probable RBD.

The prior distributions for the prevalence of each sleep apnea-RBD stratum were obtained from the NACC UDS population. The sleep apnea and RBD variables are only available for UDS version 3, thus these two potential confounders could not be included into the main analysis in Chapter Two. However, we can still use the available information as the prior distributions for the prevalence of sleep apnea and the prevalence of RBD.

Table 3.2 summarizes the prior distribution specification for each parameter used for estimating the empirical distributions of the HR_{adj}. Normal distributions for the log hazard ratios ω_1 and ω_1 were used. Dirichlet distributions for the proportion for each sleep apnea-RBD stratum among the certain treatment group were used. Distributions for the observed estimated model coefficients were taken from the Main Analysis in Chapter Two to add random sampling errors into the Monte Carlo analysis.

We drew 10,000 samples of ω_1 and ω_1 respectively from the specified Normal distributions, and 10,000 sets of samples of treatment prevalence across the sleep apnea-RBD stratum. Under Formula 1, 10,000 bias factors were computed for each treatment group respectively. Furthermore, we drew 10,000 samples of HR_{obs} for each treatment group respectively from the Normal distributions using the distributions for the observed estimated model coefficients. Thus, we were able to calculate 10,000 HRs_{adj} for each class of antidepressant. The calculated HRs_{adj} formed an empirical distribution of HR_{adj} for each class of antidepressant, and these empirical distributions are symmetrical bell-

shaped distributions (see Figure 3.1). The mean of each empirical distributions was computed as the point estimate of HR_{adj}. The 2.5th and 97.5th percentiles were found as the lower confidence limit and upper confidence limit, respectively.

3.3. Results

In this study, sleep apnea and RBD were identified as the two sources of unmeasured confounding. The estimated mean of HR_{adj} and the 95% CI for each treatment group are displayed in Table 3.3 with a comparison of HR_{obs} from the Main Analysis in Chapter Two.

In Chapter Two, a weighted Cox Proportional Hazards regression model with antidepressant treatment as the only predictor in the model was performed. Subjects reported using SSRIs, SNRIs, AAs, and TCAs at the index-visit were estimated to have 2.04 (1.69-2.48), 2.10 (1.33, 3.31), 1.46 (1.05, 2.03) and 1.58 (1.04, 2.41) times the hazard of developing dementia compared to subjects who did not report using any antidepressants at the index-visit, respectively. All estimates were significant at the 0.05 level.

In this Chapter, after adjusting for the unmeasured effects of sleep apnea and RBD, subjects who reported using SSRIs, SNRIs, AAs and TCAs at the index-visit were estimated to have 1.95 (1.59, 2.36), 1.85 (1.11, 2.91), 1.34 (0.93, 1.87) and 1.63 (1.04, 2.43) times the hazard of developing dementia compared to subjects who did not report using any antidepressant use at index-visit, respectively. All estimates are still significant at the 0.05 level. The estimates adjusted for sleep apnea and RBD are pulled towards the

null for SSRI, SNRI and AA users, but the estimates adjusted for sleep apnea and RBD remained approximately the same for the TCA users (Figure 3.1).

3.4. Discussion

In this study, sleep apnea and RBD were identified as the two major sources of unmeasured confounding in our previous analyses of antidepressant use and dementia risk. The magnitude of bias caused by the effects of sleep apnea and RBD were estimated though Monte Carlo sampling. The hazard ratios adjusted for the effects of sleep apnea and RBD were computed by dividing the hazard ratios unadjusted for the effects of sleep apnea and RBD by the estimated magnitudes of bias.

In the Main Analysis in Chapter Two, we ignored the effects of sleep apnea and RBD, thus the distribution of sleep apnea or RBD may not be comparable across treatment groups, hence the estimated effects of antidepressant on the risk of dementia may be distorted. We hypothesize that the results from the Monte Carlo analysis improved the estimates from Chapter Two towards the "true" direction by accounting for the effects introduced by sleep apnea and RBD.

The hazard ratios adjusted for sleep apnea and RBD and the corresponding 95% confidence intervals were shifted toward the null for the SSRI, SNRI, and AA users, but the point estimate of the hazard ratio adjusted for sleep apnea and RBD for the TCA users is slightly shifted away from the null (the 95% confidence interval remained approximately the same). The estimation of the effect of TCA on the risk of dementia was not sensitive to the omission of sleep apnea and RBD. In other words, sleep apnea and RBD may not be a confounder between TCA use and dementia.

This study has some limitations. First, prior distribution specifications for parameters are based on a single study for each parameter. While the studies were population-based, the populations studied may not be comparable to the NACC UDS population. An improvement could be obtaining prior distribution parameters by conducting meta-analyses. Second, proportions for each sleep apnea-RBD stratum across the treatment groups were obtained from the UDS version 3, which was initiated after 2015. Compared with the study population in this dissertation, participants in the UDS v3 subgroup were in general younger, had higher proportions for psychiatric disorders (including depression and any other types) and had higher proportions of MCI diagnosis at baseline. Thus, this subgroup was not a representative sample of the study population in this research. Finally, this study was restricted to two binary unmeasured confounders, hence insomnia is not discussed in this study. However, insomnia may be an important confounder for the association between antidepressant use and risk of dementia and should be addressed.

3.5. Conclusion

In this Chapter, the effects of sleep apnea and RBD as uncontrolled confounders between the association between antidepressant use and the risk of dementia were investigated. A bias factor formula for two binary unmeasured confounders was derived. Monte Carlo analysis was implemented to estimate the distribution of bias factor for each class of antidepressant. The effects of antidepressants on the risk of dementia adjusted for both measured and unmeasured confounders were estimated. Sleep apnea and RBD bias the estimation toward the null for the effect of SSRI, SNRI or AA on the risk of dementia.

Sleep apnea and RBD may not be a confounder on the pathway between TCA use and developing dementia. For future studies, meta-analysis could be conducted to obtain the prior distributions for parameters. Additionally, the effects of insomnia and other types of sleeping disorders can be investigated.

Table 3.1. Confounder Adjustment Status

	All Hypothetical Confounders	UDS Availability	Minimal Sufficient Set	Chapter Two	Chapter Three
Demographics	Age	√	√	√	√
	Sex	√			
	Race	√			
	Education	√			
	SES[1]				
Life Styles	Smoking	√			
	Alcohol abuse	√			
	Physical activities				
Comorbidity and Medication History	TBI[2]	√			
	Parkinson	√			
	Hypertension	√			
	Type 2 diabetes	√			
	High cholesterol	√			
	Stroke	√			
	CVD[3]	√			
	Chronic pains	√	√	√	√
	Sleep disorders		√		√
	Depression	√	√	√	√
	GDS score[4]	√	√	√	√
	Other psychiatric disorders	√	√	√	√
	CDR sum of boxes	√	√	√	√
	Cognition status	√	√	√	√
	Anti-anxiety medications	√			
Genetics	ApoE ε4 status	√		√	

[1]Socio-economic Status
[2]Traumatic Brain Injury
[3]Cardiovascular Disease
[4]Geriatric Depression Scale score

Table 3.2. Parameter Prior Distribution Specifications

	$\boldsymbol{\beta_{obs}}$[5]	$\boldsymbol{\omega_1}$[6]	$\boldsymbol{\omega_2}$[7]	$\boldsymbol{P_{X,U_1,U_2}}$[8]
Control	--			Dirichlet (1926,350,34,17)
SSRI[1]	N[9] (0.71, 0.10)			Dirichlet (331, 87, 6, 7)
SNRI[2]	N (0.74, 0.23)	N (0.53, 0.15)	N (0.79, 0.28)	Dirichlet (71, 32, 0, 5)
AA[3]	N (0.38, 0.17)			Dirichlet (135, 41, 3, 6)
TCA[4]	N (0.46, 0.21)			Dirichlet (40, 8, 1, 0)

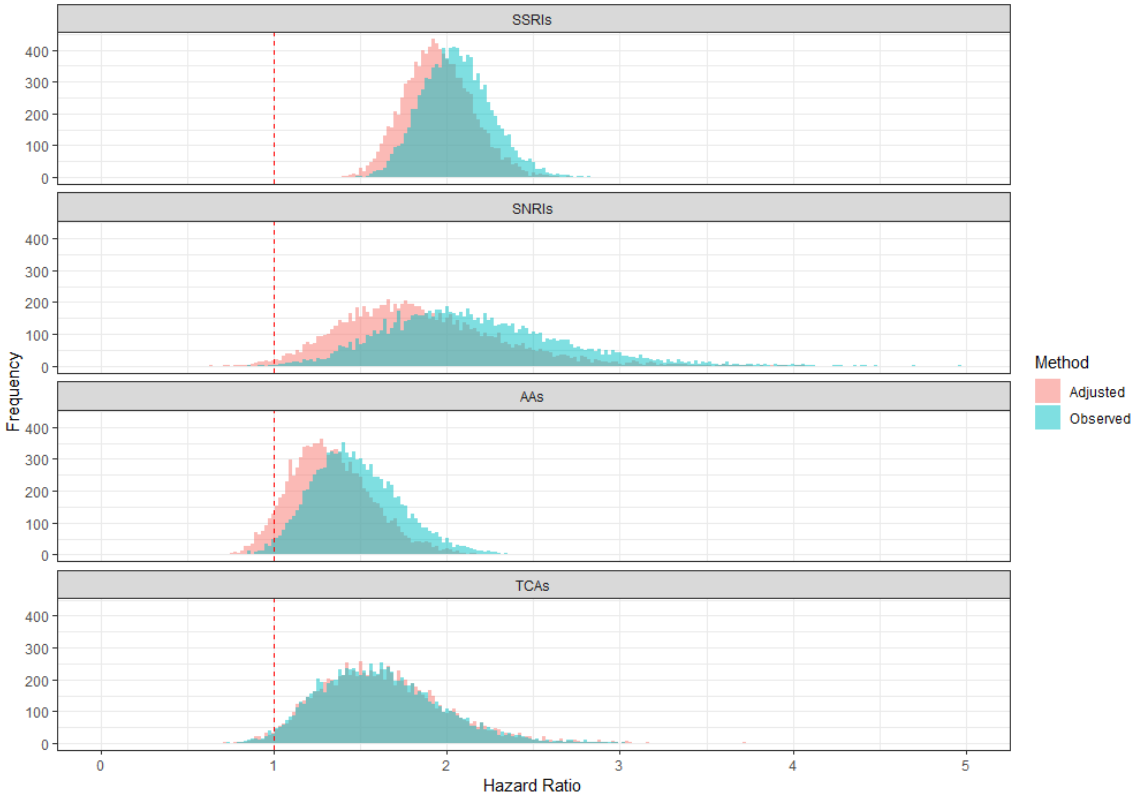
[1]Selective serotonin reuptake inhibitors
[2]Serotonin and norepinephrine reuptake inhibitors
[3]Atypical antidepressants
[4]Tri-cyclic antidepressants
[5]Observed beta coefficient from the Main Analysis in Chapter Two
[6]Log hazard ratio for sleep apnea from literature
[7]Log hazard ratio for RBD from literature
[8]Prevalence of each sleep apnea-RBD stratum in the UDS for a certain treatment group
[9]Normal distribution

Table 3.3. Estimated Bias-factor Adjusted and Observed Hazard Ratios for Dementia

	HR_{obs}	HR_{adj}
SSRI[1]	2.04 (1.69, 2.48)	1.95 (1.59, 2.36)
SNRI[2]	2.10 (1.33, 3.31)	1.85 (1.11, 2.91)
AA[3]	1.46 (1.05, 2.03)	1.34 (0.93, 1.87)
TCA[4]	1.58 (1.04, 2.41)	1.63 (1.04, 2.43)

[1]Selective serotonin reuptake inhibitors
[2]Serotonin and norepinephrine reuptake inhibitors
[3]Atypical antidepressants
[4]Tri-cyclic antidepressants

Figure 3.1. Observed and Bias-factor Adjusted Hazard Ratio Distributions



CHAPTER FOUR. RE-ESTIMATING THE EFFECTS OF ANTIDEPRESSANT USE ON THE RISK OF DEMENTIA USING MULTI-STATE MARKOV CHAIN

4.1. Introduction

The current recommendation for treating major depressive disorders is to use antidepressants over prolonged periods to relieve symptoms and prevent further episodes of depression[92,93]. The initial selection of an antidepressant medication is primarily dependent on the anticipated side effects, the safety or tolerability of these side effects for the patient, the pharmacological properties of the medication, and other factors such as patient's response to previous treatment, patient preference, insurance formulary, and cost[94]. However, psychiatrists may suggest changing the treatment regimen if poor efficacy or intolerance is observed[93]. Additionally, patients may discontinue antidepressant treatment for various reasons[95].

In previous chapters, the effects of antidepressant medication on the hazard of developing dementia were assessed assuming participants adhere to the initial treatment assignment. To briefly summarize, antidepressant use was fixed at the index-visit and intent-to-treat analysis was used. A Cox Proportional Hazards regression model with Inverse Probability Weighting was then performed to assess the hazard for developing dementia.

There are important assumptions made in the previous Cox regression analyses. First, participants were assumed to stick with the treatment assignment at the index visit until a certain event of interest occurs. Second, the hazards for developing dementia were assumed to be proportional over time. Third, participants were assumed to make only one transition from the baseline cognitive status to a certain event of interest. In other words,

the potential transitions among cognitive states prior to the occurrence of a certain event were ignored. Furthermore, we made the assumption that participants could not recover from mild impairment.

In practice, participants in the National Alzheimer's Coordinating Center are assessed annually. Cognitive status, medication use, physical and neurological examinations, and medical history are recorded at each assessment. Participants may switch or discontinue antidepressant treatments. Participants' characteristics (e.g., comorbidities, medication use, demographic information, etc.) may also change over time. Such changes may lead to time-varying hazards for developing dementia. In addition, participants may transition among different cognitive stages, such as normal cognition and mild cognitive impairment (MCI), before developing dementia. Participants may die from other causes, such as cancer, cardiovascular diseases, etc., before developing dementia, and such deaths will prevent participants from developing dementia. In the situation where the hazard of a certain health outcome is varying over time and the outcome may occur more than once, Markov models will be particularly useful[96].

In this study, we assessed the association between each class of antidepressant and the probability of dementia while accounting for the potential time-varying risks for dementia and the potential transitions among different cognitive stages before finally developing dementia. To achieve this goal, multi-state Markov models based on multinomial logistic regression were constructed.

4.2. Methods

4.2.1. Data Source and Subjects

Subjects of this study are those who participated in the annual assessment at the National Alzheimer's Coordinating Center (NACC), as known as the Uniform Data Set (UDS)[97]. The detailed description of the NACC UDS can be found in Chapter Two. Briefly, the NACC UDS was collected by trained clinicians and clinical practitioners from participants and their co-participants during in-person office visits following a standard data collection protocol. The UDS includes subjects with various levels of cognitive status: dementia caused by different reasons, different levels of cognitive impairment, and intact cognition[61]. As of September 2018, among all the UDS subjects, 35.1% were diagnosed with normal cognition, 4.3% were impaired but not MCI, 17.2% were diagnosed with MCI, and 43.4% had been diagnosed with dementia.

The following exclusion criteria were implemented for the purpose of this study. After applying these exclusion criteria, 11,939 subjects remained in the study (Figure 4.1).

1) prevalent dementia patients at the initial UDS visit;
2) prevalent antidepressant users at the initial UDS visit;
3) participants with only one UDS visit;
4) participants who were younger than 65-years-old at the initial UDS visit;
5) MAOI users or combination users at the index-visit.

4.2.2. Measurements

The methods used for measuring antidepressant use, cognitive status and other covariates for adjustment remain the same as the methods used in Chapter Two. Briefly,

participants were asked about their medication use within two-week window prior to the current UDS visit. The four classes of antidepressants identified are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tri-cyclic antidepressants (TCAs) and atypical antidepressants (AAs). Based on clinicians' assessments, cognitive status is classified into four levels: normal cognition, mild cognitive impairment (MCI), impaired but not MCI, and dementia. A series of cognitive or behavioral symptoms should be met for patients to be defined as any of the four levels of cognitive status[61]. Based on the DAG constructed in Chapter Two, covariates for adjustment included age, chronic pain, depression status, GDS score, psychiatric conditions other than depression, standard CDR sum of boxes, and the cognitive status. ApoE ε4 status was not included in the models since the results from the Sensitivity Analysis Two in Chapter Two indicated that ApoE ε4 status is not a confounder on the pathway between antidepressant use and dementia development. Subjects' treatment values, covariates values and cognitive status were assessed at every UDS visit.

4.2.3. Statistical Analysis

To evaluate the effects of different classes of antidepressants on the risk of dementia while accounting for the time-varying treatment and time-varying confounders, a multi-state Markov chain was implemented. One limitation of the estimations in Chapter Two was that treatment assignment and confounders for adjustment were fixed at the treatment UDS visit and baseline UDS visit respectively, regardless of the treatment switch in later visits or the existence of time-dependent confounders. Although we

conducted a sensitivity analysis using time-varying treatment, which supported our main results, we could not accommodate time-varying confounders. This issue can be accommodated by the multi-state Markov chain. Additionally, competing risks for the main outcome of interest, in this case death before dementia, can also be addressed by this approach, along with back transitions.

A multi-state Markov chain with three transient states (normal cognition, impaired but not MCI, and MCI) and two absorbing states (dementia and death prior to dementia) was constructed to estimate the probabilities of moving from a prior state to a current state. Subjects may move back and forth between any two of the transient states in a transition cycle, but once a subject enters an absorbing state, the subject will never exit (Figure 4.2). Although participants may die after developing dementia, those transitions were not of interest in this study. A participant's follow-up ended with entry into an absorbing state or their last active UDS visit. A subject-specific shared random effect, which was assumed to have normal distribution, was included in the models to account for the within-subject correlation[98].

Specifically, a series of three polytomous logistic regression models were built to model log-odds of the one-step transitions between any two transient states or the one-step transitions between a transient state and an absorbing state, conditioned on the prior (transient) state:

$$\text{logit}\left(\boldsymbol{P_{p,c}}(transition = 1|\boldsymbol{x}_i, \boldsymbol{z}_i, \boldsymbol{u}_i)\right) = \boldsymbol{\alpha_{p,c}} + \boldsymbol{\beta}_{p,c}^T \boldsymbol{x}_i + \boldsymbol{\gamma}_{p,c}^T \boldsymbol{z}_i + \boldsymbol{u}_i$$

Here, $\boldsymbol{x}$ is a vector of indicators for treatment; $\boldsymbol{z}$ is a vector of covariates for adjustment, and $\boldsymbol{u}$ is the subject-specific shared random effect. The subscript i refers to subject i, p refers to the prior state, and c refers to the current state. For instance, if the prior state is

normal cognition and the current state is MCI, $\boldsymbol{P_{p,c}}$ represents the probability of transition from normal cognition to MCI versus remaining in normal cognition, given values of $\boldsymbol{x}$, $\boldsymbol{z}$ and $\boldsymbol{u}$. All transitions are assumed to occur on the visit date. Any transitions among the transient states between the visits, which are not observed, are ignored.

To evaluate the predicted time for transition from one particular state to another, a Markov cohort simulation analysis was conducted using the estimated transition probabilities based on the fitted models for the one-step transitions. Times spent on transitions from baseline normal cognition to dementia and transitions from baseline MCI to dementia were estimated for each class of antidepressant assuming different baseline ages and different baseline depression statuses, while controlling for the effects of other covariates.

For the purpose of this study, transitions from and to "impaired but not MCI" were included in the model, but these results are of limited interest since the "impaired not MCI" category is quite heterogeneous. A diagnosis of "impaired but not MCI" denotes clinical impairment on cognition but does not meet criteria for MCI or dementia. The underlying causes of this impairment are unknown, and may include medical conditions, psychiatric conditions, and medication-induced cognitive dysfunction. Thus, we included this diagnosis as a state in order not to exclude data from these visits. However, it is not clear to what type of person these results would generalize. Therefore, these results are reported but not discussed in detail. All analyses were performed using PROC NLMIXED and PROC IML in SAS/STAT 9.4.

4.3. Results

Participants' had a median of four annual assessments, with an interquartile range of 2 to 7 visits. The median days between assessments was 378 days, with an interquartile range of 358 to 427 days. For purposes of describing the sample, participant characteristics were fixed at the initial UDS visit, hence no participants were yet taking antidepressants (Table 4.1). At the initial visit, the average age for this cohort of participants was 76-years-old, and more than one-third (36.8%) of these participants reported using pain medications. Additionally, about one fifth of the participants had at least one psychiatric disorder (16.6% had depression and 4.1% had any other psychiatric disorder except for depression). Most of the participants had normal cognition at entry (63.9%), while 30.1% of the participants had MCI.

During the study period, 1741 participants (14.6%) made at least one transition from normal cognition to MCI, 235 participants (2.0%) transitioned from normal cognition to dementia, and 773 participants (6.5%) died with normal cognition. Additionally, 1897 participants (15.9%) transitioned from MCI to dementia, and 534 participants (4.5%) died with MCI. Detailed one-step transition distributions are summarized in Table 4.2. In general, participants were most likely to remain in the transient state where they were previously observed. Transitions to dementia were most likely to occur from MCI. Back transitions from impaired but not MCI to normal and from MCI to normal were relatively common.

Transitions of interest are marked bold in Table 4.3. For transitions from normal cognition to MCI, SSRIs, SNRIs and TCAs were estimated to increase the probability of the transition while AAs were estimated to reduce the probability. For transitions from

normal cognition directly to dementia, SSRIs, SNRIs and AAs were estimated to increase the probability of the transition, but TCAs are associated with a significantly reduced probability. For transitions from MCI to dementia, SSRIs, AAs and TCAs are associated with increased probability for transition, but SNRIs is associated with a reduced probability for transition. The estimate for SSRI is significant. Finally, for transitions from MCI back to normal cognition, all types of antidepressant are associated with reduced odds, indicating that antidepressant use may prevent recovering from MCI to normal. Figure 4.3 displays the adjusted odds ratios and the corresponding 95% confidence intervals for transitions of interest for each class of antidepressant.

Markov cohort simulation analysis was conducted to evaluate the transition time from one particular state to another. Times spent on transitions from normal cognition to dementia and transitions from MCI to dementia for each class of antidepressant were of the primary interest. Times were estimated by assuming different baseline ages and different baseline depression status (Figure 4.4). In general, it takes longer time for transitions from normal cognition to dementia compared to transitions from MCI to dementia, regardless of the antidepressant use, baseline age or baseline depression status.

For transitions from normal cognition to dementia, different antidepressant users would spend different lengths of time in the normal state before moving to dementia. Participants in control group need the longest time to make the transition, while SNRI users need the shortest time to make the transition, assuming fixed baseline ages and depression status. SSRI users, AA users and TCA users need similar times for the transition. Baseline age and baseline depression status will further influence the times for transition. Increased baseline age would reduce the time spent in the normal state

assuming fixed treatment and fixed baseline depression status. Participants with depression at baseline will result in shorter transition times compared to participants without depression at baseline assuming fixed treatment and fixed baseline age.

For transitions from MCI to dementia, participants in comparison group would spend the longest time in the MCI state before moving to dementia while all the other antidepressant users will move to dementia quicker than the controls assuming fixed baseline age and baseline depression status. The differences in transition times among different antidepressant classes are not obvious for transitions from MCI state as they are for transitions from normal state. Increased baseline age would reduce the time spent in the normal state assuming fixed treatment and fixed baseline depression status. Participants with depression at baseline would have reduced transition times compared to participants without depression at baseline assuming fixed treatment and fixed baseline age.

4.4. Discussion

In this project, a multi-state Markov chain was implemented to evaluate the effects of antidepressants on the risk of dementia while accounting for the time-varying treatment and time-varying confounders. First, a series of three multinomial logistic regression models were built to model log-odds of the one-step transitions between any two transient states or the one-step transitions between a transient state and an absorbing state, conditioned on the prior (transient) state. Second, a Markov cohort simulation analysis was conducted using the estimated transition probabilities based on the fitted models for those one-step transitions.

The estimated effects of different classes of antidepressant on the one-step transition suggested that in general antidepressant use is associated with increased odds of moving towards the next worse cognitive status, and antidepressant use is also associated with reduced odds of moving back to the previous healthier cognitive status. In other words, antidepressant use was estimated to be associated with harmful impacts on cognition. The estimated transition times associated with each class of antidepressant illustrates the results obtained from the models. Antidepressant users would move quicker from either normal state or MCI state to demented state compared to the non-users.

As discussed in Chapter Two, there are several explanations for the potential mechanisms of the effects of antidepressants on dementia. For example, an animal study has found that SSRI treatment is associated with imbalance zinc levels, which may lead to neurofibrillary tangles, which is a marker of Alzheimer's disease and cognitive impairment[73]. Additionally, SNRI may increase user's blood pressure[64,70], and hypertension is a risk factor for vascular dementia and Alzheimer's dementia[71]. However, the association between antidepressant use and dementia may still be due to reverse causality[78], where preclinical neurodegenerative disease causes depression, which causes antidepressant initiation, which induces the association between antidepressant use and dementia.

Age is known to be a strong risk factor for cognitive decline[99]. In this study, the effects of antidepressants on transition times were impacted by different baseline ages. It would take less time for older antidepressant users to move to dementia compared with younger antidepressant users across all antidepressant classes. There have been studies suggesting that aging is associated with important changes in pharmacokinetics[100-102]. For

example, compared with the younger antidepressant users, concerns for the antidepressant users among the elderly included the differences in disposition, altered sensitivity to side effects, potential drug-drug interactions, decreased homeostatic reserve and possibly decreased sensitivity to antidepressant efficiency[102].

The effects of antidepressants on transition times would also be influenced by different baseline depression status. Antidepressant users who reported depression at baseline would move to dementia faster than antidepressant users who did not report depression at baseline across all antidepressant classes. Studies have concluded that depression is a risk factor for cognitive declines[81,82,103,104]. However, we cannot rule out the possibility that depression is merely an early manifestation, rather than a predictor, of Alzheimer's disease[82,105].

The cognitive status at the "from-state" may have impacted on the effects of antidepressant on the risk of dementia. The effects of antidepressant on transition times differ among different classes for participants in the normal state, but such differences were minimized for participants in the MCI state, although a clear difference between non-users and antidepressant users remained. We do note that the SSRI group, which was associated with increased odds of transition from normal to MCI or dementia, and from MCI to dementia, is associated with the shortest times to dementia from the normal state.

There are several advantages for this study. First, our analysis allows for time-varying treatment and time-varying confounders, hence we were able to address the potential changes of treatment regimen or participants' characteristics over time. Second, a subsequent benefit of the incorporation of time-varying treatment and confounders is that we were able to account for the time-varying hazards for developing dementia. Third,

our study permits participants to transition among different cognitive stages before developing dementia, which is usually true in practice.

There are some limitations for this study. First, all transitions are assumed to occur on the visit date, and any transitions among the transient states between the visits are ignored. Second, we cannot rule out the possibility of reverse causality, where antidepressant use is actually induced by depression as a comorbidity of preclinical neurodegeneration, rather than being a predictor of cognitive decline[78]. Third, we need to be aware that sleep disorders were not adjusted in the models due to the fact that the variables associated with sleep disorders were not properly measured for the purpose of this study.

4.5. Conclusion

In this study, we assessed the association between each class of antidepressant and the probability of dementia while accounting for the time-varying risks for dementia and the potential transitions among different cognitive stages before finally developing dementia. Multi-state Markov models based on multinomial logistic regression were constructed to model log-odds of the one-step transitions between any two transient states or the one-step transitions between a transient state and an absorbing state, conditioned on the prior (transient) state. A Markov cohort simulation analysis was conducted to evaluate the predicted time for transition from one particular state to another using the estimated transition probabilities from the estimated log-odds of those one-step transitions.

We found that in general antidepressant use is associated with increased odds of moving towards the next worse cognitive status, and antidepressant use is also associated with reduced odds of moving back to the previous healthier cognitive status. In addition, it took less time for older antidepressant users to move to dementia compared with youngers antidepressant users across all antidepressant classes. Finally, antidepressant users who reported depression at baseline would move to dementia faster than antidepressant users who did not report depression at baseline across all antidepressant classes.

There are several directions for future studies. First, more accurate measurement on transition times should be implemented. Second, in studies with longer follow-up, reverse causality can be tested by excluding incident cases within the first pre-determined number of years of treatment. Finally, the potential confounding effects of sleep disorders should be adjusted when the data is available.

Table 4.1. Summary of Subject Characteristics at the Initial Visit (N=11,939)

Variable	All subjects
Age (year)	76.0 ± 7.2
Pain meds	4397 (36.8%)
Depression	1979 (16.6%)
GDS score[1]	1 (0, 2)
Any other psychiatric disorders	483 (4.1%)
CDR[2]	0 (0, 0.5)
Cognitive status	
Normal	7625 (63.9%)
MCI[3]	3595 (30.1%)
Impaired but not MCI	719 (6.0%)
Number of assessments	4 (2, 7)
Days between assessments	378 (358, 427)

Note: Mean ± S.D. are reported for normally-distributed continuous variables. Median (Q1, Q3) are reported for non-normally-distributed variables. Frequency (%) are reported for categorical variables.

[1]Geriatric Depression Scale score
[2]Standard CDR sum of boxes
[3]Mild Cognitive Impairment

Table 4.2. One-step Transition Matrix (N=11,939)

Prior	Current				
	Normal	MCI	Impaired	Dementia	Death
Normal	29000 (88.7)	1903 (5.8)	785 (2.4)	242 (0.7)	773 (2.4)
MCI[1]	1016 (9.1)	7134 (64.2)	479 (4.3)	1941 (17.5)	534 (4.8)
Impaired[2]	619 (22.3)	572 (20.6)	1348 (59.2)	133 (4.8)	104 (3.7)

[1]Mild Cognitive Impairment
[2]Impaired but not MCI

Table 4.3. Adjusted Odds Ratios for Transitions among States

new	Prior	Current				
		Normal	MCI[5]	Impaired[6]	Dementia	Death
SSRI[1]	Normal	--	**1.25 (0.89, 1.75)**	1.42 (0.94, 2.15)	**1.23 (0.57, 2.65)**	1.27 (0.77, 2.11)
	MCI	**0.64 (0.39, 1.05)**	--	0.69 (0.38, 1.26)	**1.70 (1.28, 2.26)**	1.70 (1.08, 2.67)
	Impaired	0.83 (0.48, 1.45)	0.53 (0.28, 0.97)	--	0.52 (0.22, 1.23)	0.88 (0.36, 2.12)
SNRI[2]	Normal	--	**1.60 (0.87, 2.94)**	0.24 (0.03, 2.28)	**1.97 (0.44, 8.79)**	2.96 (1.25, 6.97)
	MCI	**0.37 (0.11, 1.21)**	--	1.26 (0.51, 3.09)	**0.57 (0.27, 1.19)**	0.87 (0.32, 2.37)
	Impaired	0.68 (0.15, 3.02)	0.49 (0.10, 2.35)	--	0.45 (0.09, 2.25)	0.20 (0.06, 0.63)
AA[3]	Normal	--	**0.71 (0.40, 1.28)**	1.23 (0.63, 2.42)	**1.06 (0.33, 3.40)**	1.45 (0.78, 2.70)
	MCI	**0.41 (0.15, 1.16)**	--	1.39 (0.60, 3.21)	**1.18 (0.68, 2.04)**	1.04 (0.52, 2.10)
	Impaired	0.65 (0.13, 3.19)	2.06 (0.64, 6.66)	--	5.12 (1.26, 20.72)	4.28 (0.99, 18.58)
TCA[4]	Normal	--	**1.23 (0.59, 3.67)**	1.46 (0.58, 3.67)	**0.16 (0.11, 0.24)**	0.93 (0.29, 3.00)
	MCI	**0.57 (0.14, 2.32)**	--	0.08 (0.05, 0.14)	**1.22 (0.51, 2.90)**	0.91 (0.24, 3.42)
	Impaired	0.45 (0.02, 8.75)	0.41 (0.02, 7.51)	--	2.69 (0.17, 43.28)	4.36 (0.59, 32.30)

Note: transitions of interest are marked bold

[1]Selective serotonin reuptake inhibitors
[2]Serotonin and norepinephrine reuptake inhibitors
[3]Atypical antidepressants
[4]Tri-cyclic antidepressants
[5]Mild Cognitive Impairment
[6]Impaired but not MCI

Figure 4.1. Study Cohort Derivation Flowchart

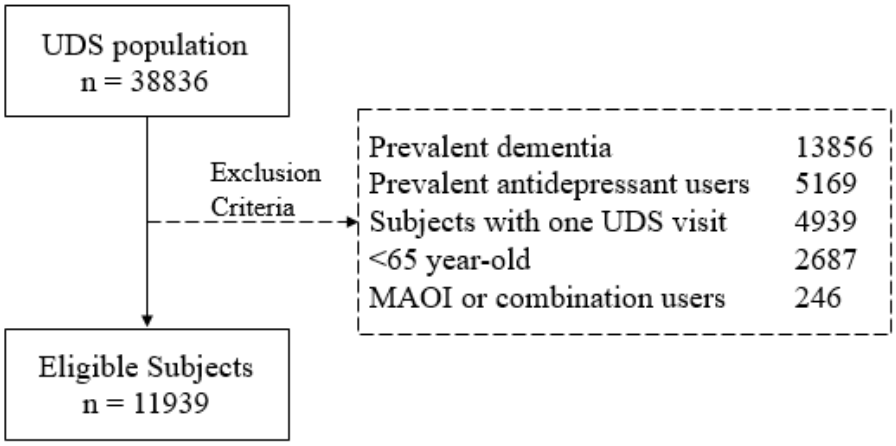


Figure 4.2. Diagram of Possible Transitions between States

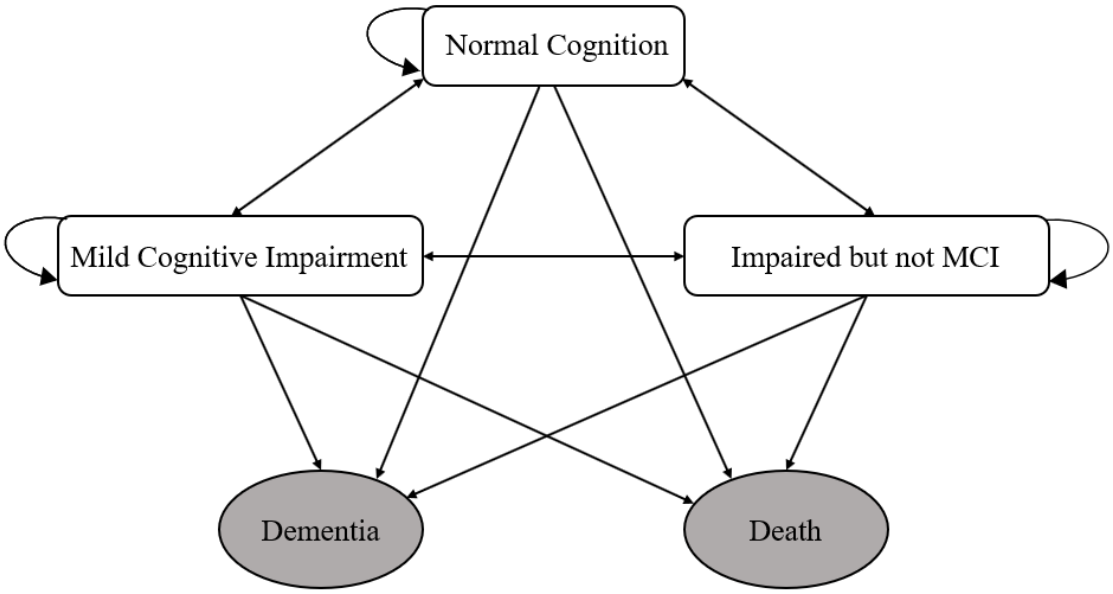


Figure 4.3. Adjusted Odds Ratios for Transitions among States of Interest

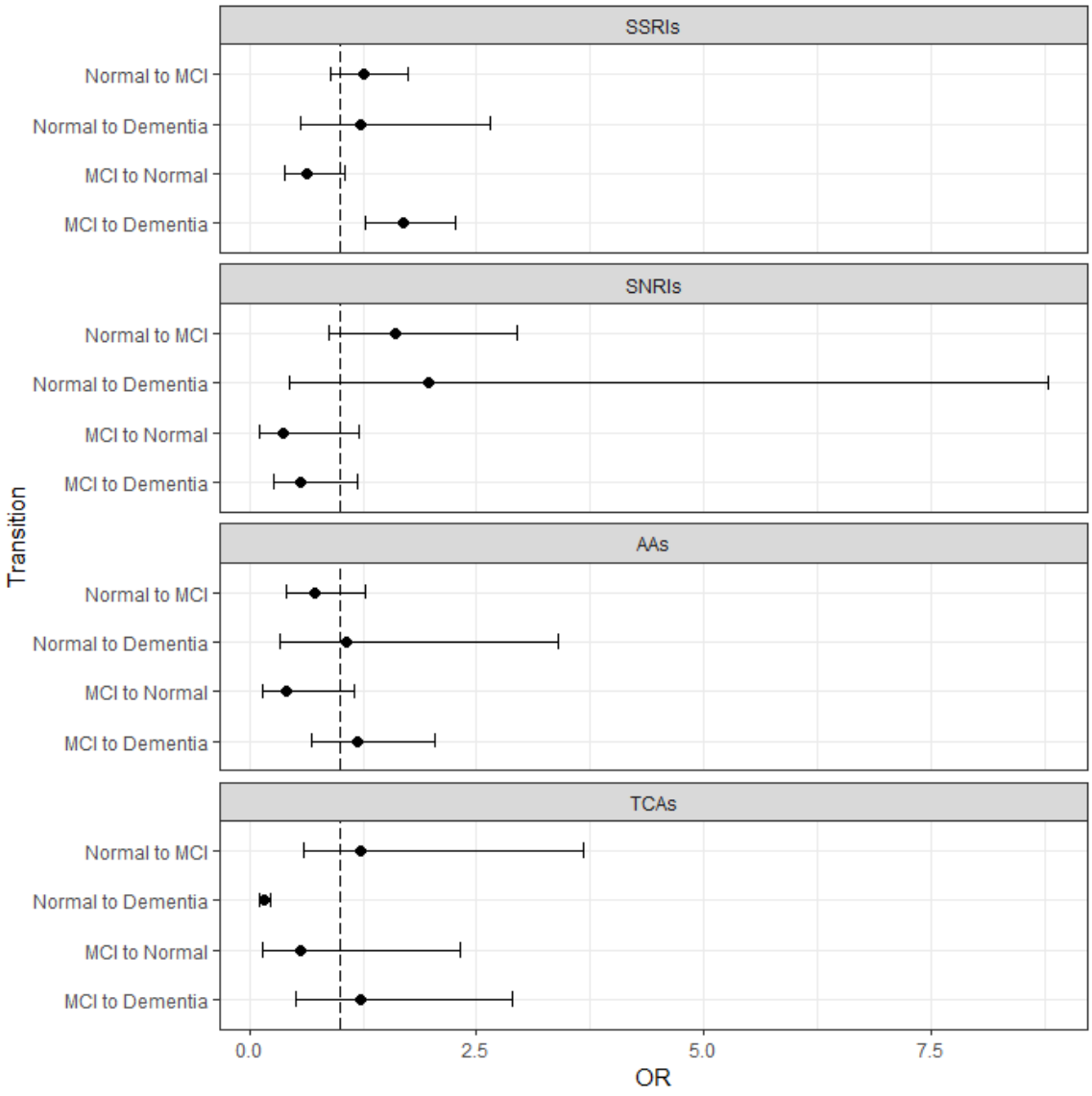
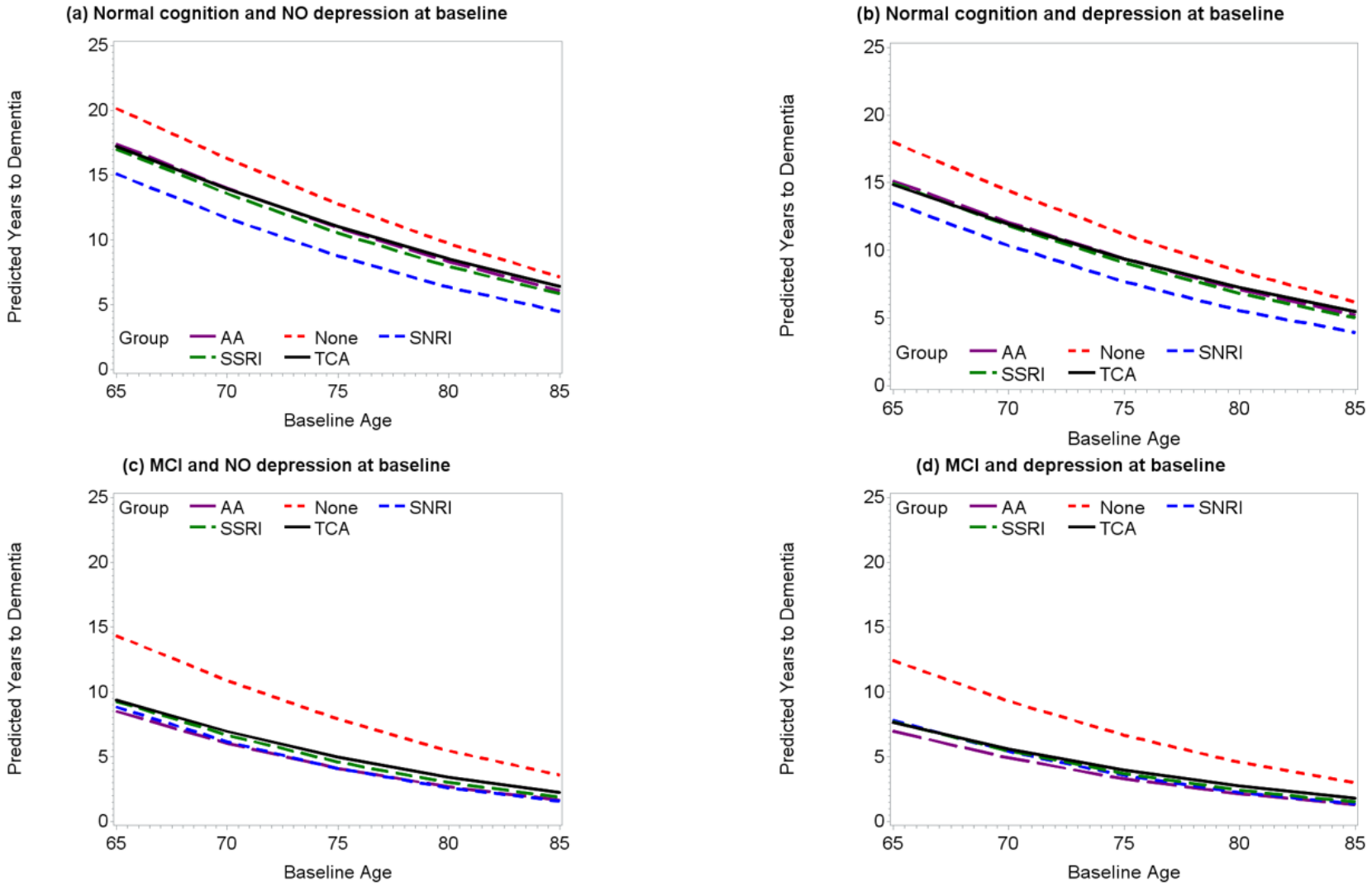


Figure 4.4. Predicted Times for Transitions of Interest



CHAPTER FIVE. CONCLUSION

5.1. Study Summary

Given the public health significances of dementia and antidepressant use among the elderly, it is important to understand the relationship between antidepressant use and dementia development in this special population. The purpose of this research is to investigate the effects of different classes of antidepressant medications on the risk of dementia using causal inference strategies using data obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS).

In Chapter Two, a new users design retrospective cohort study was conducted to evaluate the causal effects of different classes of antidepressant on the risk of dementia by performing a Marginal Structural Cox Proportional Hazard Regression Model with an Inverse Probability Weighting estimator. Significant causal effects of SSRIs, SNRIs, AAs and TCAs on the risk of dementia were observed at the 0.05 significance level. In general, the estimates were not sensitive to confounding by indication of psychiatric disorders, genetic risk due to ApoE ε4 status, or treatment regime changes in later visits.

In Chapter Three, the impacts of sleep apnea and rapid-eye-movement behavior disorder (RBD) as unmeasured confounders were assessed. Unmeasured confounding is a threat to the validity of causal inference methods. In evaluating the effects of anti-depressants, it is important to consider how common comorbidities of depression may affect both the exposure to anti-depressants and the onset of cognitive impairment. A bias factor formula for two binary unmeasured confounders was derived in order to account for these variables. Monte Carlo analysis was implemented to estimate the distribution of the bias factor for each class of antidepressant. The effects of antidepressants on the risk

of dementia adjusted for both measured and unmeasured confounders were estimated. Sleep apnea and RBD attenuated the effect estimates toward the null for SSRI, SNRI and AA on the risk of dementia. Sleep apnea and RBD may not be confounders between TCA use and dementia risk.

In Chapter Four, a multi-state Markov chain with three transient states (normal cognition, impaired but not MCI, and MCI) and two absorbing states (dementia and death prior to dementia) was built to account for the treatment changes over time and time-varying covariates. A series of polytomous logistic regression models were constructed to model the log-odds of transitions between any two transient states and transitions between a transient state and an absorbing state. A Markov cohort simulation analysis was conducted using the estimated transition probabilities from the estimated log-odds from the model results. In general, antidepressant use was estimated to be associated with harmful impacts on cognition. The estimated transition times for each class of antidepressant confirms the results obtained from the models. Antidepressant users would move quicker from either normal state or MCI state to demented state compared to the controls.

5.2. Strengths and Limitations

A major strength of this research is that we were able to simulate a "pseudo randomized study" with observational data following the intent-to-treatment principles, thus the causal effects of different classes of antidepressant could be estimated. Additionally, the potential uncontrolled confounding effects of sleep disorders were adjusted to further improve the accuracy of the estimation. Hence, our research accounts

for several limitations that previous studies in the way that the marginal effects of antidepressant on the risk of dementia were estimated, rather than the conditional effects.

Another strength of this research is that the time-varying treatment and time-varying confounders were addressed by implementing a multi-state Markov chain, hence we were able to address the potential changes of treatment regimen or participants' characteristics over time. In other words, the time-varying hazards for developing dementia were investigated in this research.

However, one subsequent limitation is that the multi-state Markov chain was only able to estimate the conditional effects of antidepressants, thus we cannot conclude causal relationship between any class of the antidepressant under investigation which potentially changes over time and the risk of dementia. Moreover, to use multi-state Markov chain, we need to assume that all transitions occurred on the visit date, and any transitions among the transient states between the visits were ignored.

Another limitation of this research is that we could not rule out the possibility of reverse causality, where antidepressant use is actually induced by depression as a comorbidity of preclinical neurodegeneration, rather than being a predictor of cognitive declines[78]. If the reverse causality is true, then the association we observed between antidepressant use and dementia may not be used for causal inference.

5.3. Future Research

There are several directions for future research suggested by the studies in this dissertation. First, we did not explore the possibility of causal inference in multi-state Markov chain due to the limited timeframe, however, this can be a direction for future

study. For example, the Inverse Probability Weighting or G-computation could be incorporated into the models to estimate the marginal effects of the treatment of interest. Second, the possibility of reverse causality should be checked. In this study, the follow-up time was not long enough to assess the possibility of reverse causality, however, for studies with decades of follow-up, incident cases that arise in the first pre-determined number of years of treatment can be excluded to test the reverse causality hypothesis[79]. Finally, the medication measurement is not accurate in the UDS. In future studies, better measurements are expected. For example, during the UDS visit, participants were only asked if they were using any medication within two weeks before the current visit. Thus, details about the doses or indications associated with the reported medications were not available. Besides better measurements on the exposure, more accurate measurements on the timings of cognitive transition are needed to better estimate the impacts of some certain exposure on cognitive declines, and measurements on risk factors such as physical activities and diet habits should be implemented.

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