ESTIMATING THE EFFECTS OF Z-DRUGS ON THE RISK OF COGNITIVE IMPAIRMENT

Xuan Zhang
University of Kentucky, xuanzhang92@uky.edu
STUDENT AGREEMENT:

I represent that my thesis or dissertation and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained and attached hereto needed written permission statements(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine).

I hereby grant to The University of Kentucky and its agents the non-exclusive license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless a preapproved embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student’s advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student’s dissertation including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Xuan Zhang, Student

Erin Abner, PhD, Major Professor

Dr. Erin Abner, Director of Graduate Studies
ABSTRACT OF CAPSTONE

Xuan Zhang

The College of Public Health

University of Kentucky

2018
ESTIMATING THE EFFECTS OF Z-DRUGS ON THE RISK OF COGNITIVE IMPAIRMENT

ABSTRACT OF CAPSTONE

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

By:
Xuan Zhang
Lexington, Kentucky

Director: Erin Abner
Lexington, Kentucky

Copyright © Xuan Zhang 2018
ABSTRACT OF CAPSTONE

ESTIMATING THE EFFECTS OF Z-DRUGS ON THE RISK OF COGNITIVE IMPAIRMENT

Background: Dementia and sleep disorders are two significant health problems in older adults. Studies suggest that sleep disorders and their treatment might associate with the risk of dementia. Z-drugs are one of the most widely used prescription hypnosedatives in the United States (US) for insomnia in addition to benzodiazepines (BZDs). Studies have shown that BZDs are associated with dementia among senior users. Study Aim: The purpose of this study is to evaluate the association between Z-drug initiation and cognitive impairment among the elderly in the US. Study Design and Data Source: We conducted a retrospective cohort study with a new user design using the Uniform Data Set (UDS) from the National Alzheimer’s Coordinating Center (NACC) from 2005-2017. Methods: We performed Inverse Probability of Treatment Weighting (IPTW) based on propensity scores generated from data obtained at the study baseline and Incidence Density Sampling (IDS) for the non-user control selection. Descriptive analysis, repeated measures general linear regression, and survival analysis were performed to estimate the crude and adjusted risk of Z-drug use and cognitive impairment. Results: The neuropsychological
outcomes were measured by the Mini-Mental State Examination (MMSE),
Clinical Dementia Rating (CDR) sum of boxes, and Trail Making Test (TMT) A
and B. The decreased MMSE, increased CDR summary score, and the
increased Trail A and Trail B test scores within user groups indicated that
cognitive function declined over time among the UDS participants regardless of
the hypnosedative initiation (P<0.05). The significant difference in the change in
the Trail B test score among Z-drug users compared to non-users suggested that
Z-drug users had a slower decline in the Trail B test one and two years after
initiation (P<0.05). Z-drug users also had a worse survival rates than BZD-users
from one year after initiation in the Kaplan-Meier analysis (P<0.05).

Conclusions: Most neuropsychological tests showed decline in global cognitive
and executive function among users and non-users during follow-up. Z-drug
users had a slower decline in executive function than non-users over time but
worse survival rates than BZD-users one year after initiation. Future studies with
a prospective study design may further explore the drug-outcome association
and the dose-response relationship.

KEYWORDS: Prescription hypnosedatives, Z-drugs, benzodiazepines, insomnia,
sleep disorders, dementia, cognitive impairment, executive function, propensity
score, IPTW, incidence density sampling

Xuan Zhang

November 5, 2018
ESTIMATING THE EFFECTS OF Z-DRUGS ON THE RISK OF COGNITIVE IMPAIRMENT

Xuan Zhang

College of Public Health

University of Kentucky
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>v</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>vii</td>
</tr>
<tr>
<td>CHAPTER 1: INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Dementia and reversible dementia</td>
<td>1</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>2</td>
</tr>
<tr>
<td>Prescription hypnosedatives and dementia</td>
<td>7</td>
</tr>
<tr>
<td>Research gap</td>
<td>8</td>
</tr>
<tr>
<td>Study aim and hypothesis</td>
<td>11</td>
</tr>
<tr>
<td>CHAPTER II: METHODS</td>
<td>13</td>
</tr>
<tr>
<td>CHAPTER III: RESULTS</td>
<td>25</td>
</tr>
<tr>
<td>CHAPTER IV: DISCUSSION AND LIMITATIONS</td>
<td>35</td>
</tr>
<tr>
<td>CHAPTER V: IMPLICATIONS FOR PUBLIC HEALTH</td>
<td>43</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>49</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>58</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1a, Participants’ characteristics at study baseline, NACC, 2005-2017 ..... 58
Table 1b, Cognitive test means at baseline and during follow up, NACC, 2005-2017 .................................................................................................................................................. 59
Table 2a, Z-drug effects on cognitive change, vs. BZD-users, one year after initiation ........................................................................................................................................... 60
Table 2b, Z-drug effects on cognitive change, vs. BZD-users, two years after initiation ........................................................................................................................................... 60
Table 2c, Z-drug effects on cognitive change, vs. BZD-users, one and two-year change trajectory ........................................................................................................................................... 60
Table 3a, Z-drug effects on cognitive change, vs. non-users, one year after initiation ........................................................................................................................................... 61
Table 3b, Z-drug effects on cognitive change, vs. non-users, two years after initiation ........................................................................................................................................... 61
Table 3c, Z-drug effects on cognitive change, vs. non-users, one and two-year change trajectory ........................................................................................................................................... 61
LIST OF FIGURES

PAGE

Figure 1a, Study scheme ........................................................................................................ 62
Figure 1b, Participants selection examples ........................................................................... 63
Figure 2, DAG for the association between Z-drug use and cognition ................................. 64
Figure 3a, Propensity score distributions by treatment group, Z-drug users vs. BZD-users ............................................................................................................................. 65
Figure 3b, Propensity score distributions by treatment group, Z-drug users vs. non-users, IDS .......................................................................................................................... 66
Figure 4a, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. BZD-users, MMSE ................................................................. 67
Figure 4b, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. BZD-users, CDR sum of boxes ........................................ 67
Figure 4c, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. BZD-users, Trail Making Test – Trail A .......................... 68
Figure 4d, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. BZD-users, Trail Making Test – Trail B .................. 68
Figure 5a, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. non-users, MMSE ................................................................. 69
Figure 5b, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. non-users, CDR sum of boxes ........................................ 69
Figure 5c, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. non-users, Trail Making Test – Trail A .... 70
Figure 5d, Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. non-users, Trail Making Test Trail B .... 70
Figure 6a, Kaplan-Meier Analysis Z-drug users vs. BZD-users ......................... 71
Figure 6b, Kaplan-Meier Analysis Z-drug users vs non-users ......................... 72
ACKNOWLEDGEMENTS

This work would not have been possible without the support of my committee members at the University of Kentucky Sanders-Brown Center on Aging, the College of Public Health, and the College of Pharmacy. I first and foremost would like to thank my committee members Dr. Erin Abner, Dr. Daniela Moga, and Dr. Steve Fleming for their guidance, expertise, and patience. Dr. Abner, thank you for your mentorship and support throughout my DrPH training, my work at Sanders-Brown, and advices for my future career and life. I am grateful for your mentorship and friendship over the years and I hope we will maintain these in the future. Dr. Moga, thank you for guiding me into pharmacoepidemiology and believing in my ability to take on this project. I am also grateful for your guidance and friendship since the project started in your class two years ago. The class gave me a new insight into research on epidemiology. Dr. Fleming, thank you for your guidance for graduate training in epidemiology and in this project. I further developed my critical and independent thinking about chronic epidemiology as a doctoral level student in your class. Your way of teaching encouraged me to evaluate research projects and publications through independent thinking with confidence and to share my thoughts with other researchers and professionals.

I would also like to acknowledge the Sanders-Brown Center on Aging at the University of Kentucky for the endless opportunities that allowed me to integrate my clinical background and to further develop my public health skillset to become a public health professional today. I would like to thank faculty and colleagues at Sanders-Brown for their mentorship, guidance, friendship, and coordination in
providing training opportunities throughout my study and work since 2016. I would like to especially thank Dr. Gregory Jicha at the clinical core for his academic and clinical mentorship during my DrPH practicum. I would also like to thank Dr. Richard Kryscio, Dr. Frederick Schmitt, and Dr. Richard Ronan Murphy for their guidance in research and clinical practice and the pleasure of collaborating the aging-related projects. I am grateful to have Omar Al Janabi, Justin Barber, Tim Shannon, and Josh Stalion as my colleagues. Thank you for all your friendship and support throughout my study and work at Sanders-Brown.

To the University of Kentucky, thank you for showing me the “Big Blue Nation” spirit. I would like to thank the University of Kentucky Writing Center for their help in reviewing my manuscripts throughout my DrPH program. I would like to especially thank Tyler Kibbey from the Writing Center in helping me improve the language of this project. To the College of Public Health, thank you for the opportunity that allowed me to further develop my public health skills to an advanced level. To my professors, thank you for teaching me and equipping me with the knowledge that I will use going forward in my career. I would like to thank Dr. Graham Rowles, for your believing in me and guidance in my research and career development in gerontology and aging. To my cohort and classmates, thank you for your encouragement and friendship during this program.

To my colleagues, professors, and friends at the Johns Hopkins University where I started my pursuit of a career in public health in the United States, thank you for your guidance, encouragement, and strong belief in me. And finally, to my parents from China and family in-law in Maryland, thank you for being my biggest
supporters while I was making an important transition in my life. I would also like to especially thank my husband, Michael, for the suggestions and great ideas for the graphic improvement.
CHAPTER 1
INTRODUCTION

Dementia and sleep disorders are two significant health problems in older adults. Studies suggest that sleep disorders and their treatment might associate with the risk of dementia.

**Dementia and Reversible Dementia**

*Dementia Definition, Types, and Prevalence*

Dementia is a clinical syndrome characterized by “a global deterioration of mental function in its cognitive, emotional, and cognitive aspects.” Dementia typically is a cognitive decline with a long period of progression, which often includes memory, leading to disability in elderly people. Alzheimer’s disease (AD) is the most common type of dementia, followed by vascular dementia, frontal lobe dementia, and dementia with Lewy bodies. Reversible dementias are conditions that may be associated with cognitive or behavioral symptoms but are not always sufficient to meet the clinical dementia diagnosis. Furthermore, dementias due to medications and other clinical conditions such as normal pressure hydrocephalus, thyroid dysfunction, and depression may be reversible. Reversible dementias could be treatable but should not be assumed as fully reversible. Dementia due to hypnosedative exposure could be considered as reversible. Most common types of dementias due to degenerative and vascular pathology may not be reversible.
Based on the current epidemiological report, the estimated prevalence of dementia is 3.9% in people over 60 years of age, and the estimated incidence of dementia is approximately 7.5 per 1000 people per year worldwide. The incidence of dementia ranges from approximately 1 per 100 person-years in people aged 60-64 years to >70 per 1000 person-years in people older than 90 years. Based on estimates from the Aging, Demographics, and Memory Study (ADAMS), 14% of people age 71 and older in the US have dementia. Additionally, an estimated 5.7 million Americans of all ages are living with AD in 2018. For people who are 65 years and older, one in 10 of them has AD in the US.

**Dementia risk factors & Hypnosedatives and Dementia**

The risk factors for dementia include non-modifiable and modifiable factors. Non-modifiable factors include age, family history, and the APOE-ε4 genotype. Whereas, modifiable risk factors include cardiovascular comorbidity risk factors, education, social and cognitive engagement, traumatic brain injury (TBI), diabetes mellitus, cerebrovascular diseases, alcohol consumption, and tobacco use. In addition to these risk factors with well-confirmed evidence, there are also modifiable risk factors that may contribute to cognitive impairment or dementia without sufficient scientific evidence, such as sleep disorders and hypnosedatives.

**Sleep Disorders**

Sleep Disorders Definition, Types, and Significance
Clinical sleep disorders typically include insomnia, sleep apnea, parasomnias, restless leg syndrome, and narcolepsy.\textsuperscript{11-13} These disorders occur due to a variety of reasons including allergies and respiratory problems, nocturia, chronic pain, stress, and anxiety.\textsuperscript{14} Insomnia, sleep apnea, and parasomnias are the most common sleep disorders associated with cognitive impairment.\textsuperscript{12,15,16}

Specifically, insomnia, one of the most common sleep disorders, refers to dissatisfaction with sleep quantity or quality, usually including “difficulty falling asleep, frequent nightmare awakenings with difficulty returning to sleep, and/or awakening earlier in the morning than desired.”\textsuperscript{17,18} Insomnia lasts for a month or longer, and most of the insomnia cases are secondary - they are the symptom or side effect of certain medical conditions, medicines, sleep disorders, and substances.\textsuperscript{19} Insomnia can associate with daytime sleepiness and a lack of energy, which may also cause trouble focusing on tasks, paying attention, and remembering life events.\textsuperscript{18} Another common sleep disorder which often influences cognitive impairment and the quality of life of older adults is sleep apnea. Sleep apnea is defined by “the occurrence of daytime sleepiness, loud snoring, witnessed breathing interruptions, or awakenings due to gasping or choking in the presence of at least five obstructive respiratory events (apneas, hypopneas or respiratory effort related arousals) per hour of sleep.”\textsuperscript{20} Besides, parasomnia is a disorder characterized by abnormal or unusual behavior of the nervous system during sleep, including non-rapid eye movement (NREM)-related parasomnias, rapid-eye movement (REM) sleep disorder, and other parasomnias.\textsuperscript{21} REM sleep order is often seen in older adults.\textsuperscript{22}
Furthermore, restless leg syndrome (RLS), which is also called Willis-Ekbom Disease, commonly occurs in the late afternoon or evening hours and is most severe at night. RLS usually causes unpleasant or uncomfortable sensations in the legs and an irresistible urge to move them. As a result, people with RLS could have difficulty falling asleep or waking up easily. Another sleep disorder, narcolepsy, affects the brain's ability to control sleep-wake cycles. People with narcolepsy usually feel rested after waking but then feel sleepy throughout the day.

Clinical sleep disorders do not only induce fatigue, but also have a negative impact on health and quality of life. Chronic sleep disorders affect approximately 30% of adults, and older adults are even more susceptible. The elderly have a higher prevalence of insomnia due to medical illness, psychiatric conditions, side effects from medication, circadian rhythm changes, sleep disorders, and psychosocial factors. Insomnia in older adults has been associated with an increased risk of health problems, including dementia, depression, acute myocardial infarction, hypertension, diabetes, and disability. However, sleep disorders are often self-reported by individuals to health professionals or researchers, and it can be difficult to ascertain sleep disturbance. For example, people who have sleep disorders may not report the condition because they are under good control with sleeping aids or are unaware of the severity of their condition.

Non-medication treatment of sleep disorders
Treatment of sleep disorders involves lifestyle interventions, medical devices, and medications.\textsuperscript{12,13} For lifestyle interventions, maintaining a healthy diet and appropriate exercise, sticking to a regular sleeping schedule, limiting caffeine intake, decreasing tobacco and alcohol use, and avoiding high carbohydrate meals before bedtime help improve the quality of sleep.\textsuperscript{12,31} Breathing devices, such as continuous positive airway pressure (CPAP), help with sleep apnea by continuously maintaining mild air pressure to keep the airways open in people who have breathing issues.\textsuperscript{32} Medication interventions include sleeping pills, melatonin supplements, allergy or cold medication, and medications for underlying health issues.\textsuperscript{12,13} Due to their high prevalence of sleep disorders, use of sleep medications is frequent among the elderly frequently.\textsuperscript{27}

\textit{Medication treatment of sleep disorders}

Commonly used medications for sleep disorders, especially insomnia, sleep apnea, and parasomnia, are prescription hypnosedatives. Use of prescription hypnosedative drugs, which are defined as benzodiazepines (BZDs) and benzodiazepine-like hypnotics, is currently a focus of research and clinical practice. BZDs have been preferred for the treatment for insomnia.\textsuperscript{12,30} The commonly prescribed BZDs include alprazolam, chlordiazepoxide, diazepam, and lorazepam.\textsuperscript{33} The newer non-benzodiazepine hypnosedatives, the so-called “Z-drugs”—zopiclone, zolpidem, and zaleplon are also commonly used.\textsuperscript{12,30} Studies report that the negative impact of the use of hypnosedatives increases with age since older adults are at a higher risk for impaired cognitive and motor
Among the sleep disorders described above, insomnia, sleep apnea, and parasomnias are the most common chronic sleep disorders that are potentially associated with Z-drug use and cognitive impairment.\textsuperscript{35,36}

**BZD & Z-drug pharmacokinetics and indications**

BZDs and Z-drugs have similar inhibitory effects on the central nervous system, with slight differences in indications due to their pharmacological mechanisms.\textsuperscript{33-35} BZDs are used for numerous indications, including anxiety, insomnia, muscle relaxation, relief from spasticity caused by central nervous system pathology, and epilepsy.\textsuperscript{37} BZDs enhances the action of the inhibitory neurotransmitter- Gamma Aminobutyric Acid (GABA).\textsuperscript{33} GABA is the most common neurotransmitter in the central nervous system.\textsuperscript{37} GABA is inhibitory: by reducing the excitability of neurons, GABA produces a calming effect on the brain.\textsuperscript{37} The hyperpolarization of the postsynaptic membranes in an inhibitory synapse make the postsynaptic neuron less excitable.\textsuperscript{38,39} The GABA-A receptor is a ligand-gated chloride-selective ion channel.\textsuperscript{38} Binding of BZDs to GABA-A receptor allosterically enhances binding of GABA.\textsuperscript{37,38} Therefore, the closed chloride channel is open and the cell further hyperpolarizes, making the neuron less excitable.\textsuperscript{37,38} The half-life of BZDs range from one hour to 250 hours in general.

Similarly, Z-drugs also interact with the GABA-A receptor to enhance the inhibitory action of GABA.\textsuperscript{40} The Z-drugs are non-BZD hypnotic agents belonging to the imidazopyridine family.\textsuperscript{6} Z-drugs, which are short-acting GABA agonists,
have only been approved for the treatment of insomnia.\textsuperscript{6,35,41} For example, zolpidem acts as an agonist of the BZD-ω\textsubscript{1} receptor component of the GABA-A receptor complex and is commonly used in patients with insomnia, including elderly patients.\textsuperscript{6} Comparing to BZDs, Z-drugs have a rapid onset, short duration of action (the peak time is 2 hours, half time is 1.5-5.5 hours), low tolerance, and a low incidence of adverse effects for insomnia treatment.\textsuperscript{6,7}

**Prescription Hypnosedatives and Dementia**

The severity of hypnosedative-induced side effects causes physicians to exercise caution.\textsuperscript{40-42} BZD and other non-selective GABA agonists with hypnotic effects similar to those of zolpidem have been shown to disrupt memory in both human participants and animal subjects.\textsuperscript{43} BZD use alone has been associated with cognitive impairment.\textsuperscript{42,44-46} However, the possibility that Z-drugs, used independently of BZDs, increases the risk for dementia has only been indicated by limited outcome measures and regular observational study designs.\textsuperscript{5}

Specifically, studies showed that BZDs are associated with an increased risk of dementia in the elderly population, and these risks decreased when BZD use was discontinued.\textsuperscript{47-51} In a population-based case-control study by Billioti de Gage et al., BZD use was associated with increased odds of AD (OR=1.51, 95% CI: 1.36-1.69) compared to non-users among people aged >66 years old in a community in Canada from 2000 to 2009.\textsuperscript{52} In addition, neuropsychiatric adverse events have been reported among Z-drug users, including hallucinations, amnesia, and parasomnia.\textsuperscript{40} Longitudinal studies have also reported increased
risk of dementia among older adults with long-term insomnia. A study in Taiwan by Chen et al. showed that patients with long-term use of hypnotics have more than two times of increased risk of dementia, especially those aged 50 to 65 years. The study also showed increased risks of dementia among those with long-term insomnia diagnoses after adjusting for relevant chronic cerebrovascular conditions (i.e. hypertension, diabetes mellitus, hyperlipidemia, and stroke).

Meanwhile, adverse effects associated with Z-drugs include nausea, headache, dizziness, drowsiness, hallucination and short-term memory loss and other psychomotor impairment. As a result, the risk of falls and hip fractures is also likely. The residual effect of Z-drugs on next-day cognitive and psychomotor behavior has significant impact on lifestyle, safety, and occupational considerations, including motor vehicle and machine operation. A three-week clinical trial revealed psychomotor retardation in 2% of patients receiving zolpidem and in 0% of patients in the placebo group. However, there are limited clinical data concerning the effects of long-term Z-drug use on psychomotor or cognitive functions. Thus, the relationship between the use of Z-drugs and the potential risk of cognitive impairment remains unknown.

Research gap

It is unclear whether sleep disorder itself, the hypnosedative use, or both increase the risk of cognitive impairment. The association between hypnosedative use and cognitive impairment is undetermined based on the
current studies. However, prescription hypnosedatives are still commonly applied in clinical practice for significant reasons.

Whether or not sleep disorder alone is a risk factor of cognitive impairment, clinicians would still prefer prescribing hypnosedatives to make notable improvement in sleep and quality of life for people with sleep disorders. For example, studies have demonstrated that the use of BZDs is associated with an improvement of sleep duration.\textsuperscript{54} However, BZDs are less effective in reducing sleep latency with prolonged side effects of drowsiness, dizziness, and cognitive impairment.\textsuperscript{55} Alternatively, zaleplon is effective in improving sleep latency (time needed to fall asleep) with a rapid onset, short duration of action, and low tolerance.\textsuperscript{27} For example, zaleplon significantly reduced sleep latency by 22 minutes among the elderly with insomnia in current studies.\textsuperscript{56,57} If some hypnosedatives are more likely to have adverse effects (e.g., cognitive impairment) in patients, using alternatives may reduce the risk of undesirable effects. Stranks et al. illustrated that the side effect profile associated with Z-drugs were more benign than those related to the BZDs.\textsuperscript{58} However, there are limited studies to ascertain the long-term adverse effects, including cognitive effects, of Z-drugs. Z-drugs have its restrictions in improving sleep disorders too. For instance, the improvement of sleep maintenance (duration and number of awakenings) and sleep quality with Z-drugs is controversial.\textsuperscript{27,56} Therefore, it is important to examine which treatment method has fewer side effects among older adults regarding their comorbidities and other health conditions.\textsuperscript{30}
Additionally, although prior studies have shown a potential risk for incident dementia among older adults using BZDs and Z-drugs, few of them have examined long-term hypnosedative use on cognitive changes. Since dementia has a long pre-clinical latent period, the current studies may not lasted long enough to capture dementia diagnosis. It is possible that people who do not develop dementia may still experience cognitive impairment. Detecting the cognitive impairment and making early medical decisions are also essential in dementia prevention and intervention.

Furthermore, the association between hypnosedative use and cognitive impairment will be distorted by confounding by indication (e.g., insomnia) if only comparing cognitive impairment between hypnosedative users and non-users. For example, people take hypnosedatives for their insomnia and people who do not take hypnosedatives if they do not have insomnia. If insomnia is associated with cognitive impairment, users may experience worse cognitive impairment than non-users due to insomnia rather than the use of hypnosedatives. Also, many studies include prevalent users instead of new users in studying cognitive impairment, which might have led to distortion of the results because of the mixed effects of different drugs, attrition bias, or recall bias. For example, if subjects who took Z-drugs for several years recently switched to BZDs when they joined in a study, they could be assigned to the BZD treatment group. However, these individuals may still be under the influence of Z-drugs. This misclassification may decrease the difference on cognitive impairment between Z-drug users and BZD-users.
Further, comparing the effects of prescriptive hypnosedative users and non-users will not capture the difference between BZDs and Z-drugs if both types of hypnosedatives are included as one comparison group in the study. Most research has studied the effect of BZDs on cognitive impairment or BZDs and Z-drugs together, so research with Z-drug users only is limited.

Additionally, using prevalent users who may have been on hypnosedatives for a long time as a comparison group may introduce healthy initiator and healthy adherer bias. The healthy initiator bias comes from the selective initiation of preventive treatments among healthy and health-conscious patients and the selective channeling of treatments away from frail individuals who are at a higher risk of adverse outcomes. The healthy adherer bias extends the healthy initiator and frailty bias to patients who adhere to treatment, which are more likely to adhere to other healthy behaviors and preventative care and are less likely to have experienced changes in frailty. These two situations may distort the drug-outcome association so that treatment looks "beneficial".

Study Aim and Hypothesis

In the current research, we will conduct a new user design study among a retrospective cohort of older adults (≥65 years) from the National Alzheimer’s Coordinating Center (NACC). The new user design will allow us to evaluate the effect of prescription hypnosedative use for more than one year on cognitive impairment by comparing cognitive change between Z-drug users, BZD-users,
and non-users. We will examine the effects of Z-drugs and BZDs on the risk of
cognitive impairment and specific cognitive domains (e.g., executive function)
among long-term users one or two years after drug initiation. We hypothesized
that Z-drug users will have a higher risk of cognitive impairment than non-users
and a lower risk of cognitive impairment than BZD-users.
CHAPTER 2

METHODS

Study Population, Inclusion and Exclusion Criteria

The target population was adults who were 65 years and older in the US population who may use prescription hypnosedatives. Participants in the current study were drawn from the Uniform Data Set (UDS) database of the National Alzheimer’s Coordinating Center (NACC). NACC aggregates mandated standard data elements (the UDS) collected by all federally funded Alzheimer’s Disease Centers (ADC). Most ADC participants in the dataset are evaluated annually until their death, after which the majority of participants are evaluated via autopsy. The NACC started to aggregate UDS data from the ADCs beginning in 2005, with the ADC participants representing the range of cognitive status: normal cognition, mild cognitive impairment (MCI), and dementia. Trained clinicians and clinical personnel collect data from subjects and their co-participants (usually a close friend or a family member). A consensus team or a single physician makes the cognitive diagnosis. Information is collected during in-person office visits, home visits, and telephone calls. In our retrospective cohort study, we drew clinical UDS data from the May 2017 data freeze. Initial inclusion criteria were participants who were at least 65 years at the initial UDS visit; were cognitively normal at the initial visit; had at least one follow-up UDS visit; and reported no use of Z-drugs or BZDs at the initial visit. This yielded an initial sample of 8,136 participants (Figure 1a).
The UDS database contains demographic characteristics, cognitive test results, and clinical diagnoses of cognitive status: Normal cognition, Impaired but not Mild Cognitive Impairment, Mild Cognitive Impairment, and Dementia. The diagnostic criteria were uniform across ADCs and were determined based on the most frequently used clinical diagnostic criteria, scales for the features of AD, and neuropsychological measures from all ADCs. Detailed information about the UDS study population is available in other literature.

The database also contained self-reported medication use, including the exposure of interest: hypnosedative use. Specifically, names of medications used within two weeks of the UDS visit were recorded by ADCs, so it is possible that exposure may not be captured in the database if a participant failed to report a medication. It is also important to note that ADCs may collect this information in a variety of different ways. They might have participants bring their medications or a list of medications they were taking within two weeks of UDS visit to the research assessment, or they may rely on participants’ memory to report medications. Other important limitations to note regarding the medication use data: indication for use, duration, and dose are not recorded in the database.

We excluded participants who had missing data on medication use at the initial UDS visit. We did not exclude participants with mental disorders (e.g., anxiety, depression, and psychotic disorders) since the majority of mental diagnosis information was missing in our dataset. We did not exclude “impaired but not MCI” or participants with dementia due to the limited sample size at the
study baseline (the UDS visit before hypnosedative initiation). We selected new users who did not report hypnosedative use at their initial UDS visit. Then participants were assigned to Z-drug user group or BZD-user group based on which drug they firstly reported at subsequent UDS visits. We also added a non-user group as controls for the Z-drug users with the incidence density sampling procedure and with a four-fold match to Z-drug users by the year of their UDS enrollment.

**Study Design**

Our study was a dynamic cohort study with the study baseline defined as the visit immediately prior to that at which new users reported their initiation intake of hypnosedatives. We performed a new user design to reduce potential biases. In addition to selecting the group of new Z-drug users, we selected a group of BZD-users as well as a group of non-users of hypnosedatives. We compared Z-drug new users to BZD new users in order to mitigate confounding by indication. In addition to confounding by indication, the new user design will also reduce the healthy initiator bias and healthy adherer bias which may distort the drug-outcome association in observational studies.

*The New User Design*

The Active Comparator New User Design (ACNU) was developed to avoid the biases mentioned above. ACNU is regarded as the standard for pharmacoepidemiology. Furthermore, ACNU emulates the intervention part of a randomized control trial (RCT). The ACNU include cohorts of new drug
users, followed over time for the health outcomes of interest.\textsuperscript{9,60} Comparison
groups are individuals newly prescribed an index drug versus individuals newly
prescribed a therapeutic alternative or comparator drug.\textsuperscript{9,60} In our study, the
index drug was the Z-drug and the comparator was BZDs. To compare with
results using traditional user versus non-user design, we also added a non-user
group as a modification of the ACNU.

\textit{Exposure and measures}

Exposure status was determined at the study baseline according to the
drug intake status: Z-drug initiation, BZDs initiation, and non-initiation. There
were two comparisons in our study: Z-drug new users versus BZD new users,
and Z-drug new users versus non-users of either BZDs or Z-drugs. We selected
new users who did not report hypnosedative use at their initial UDS visit but
reported initiation of Z-drug or BZD at subsequent UDS visits. We selected non-
users using the incidence density sampling method.

\textit{Incidence Density Sampling for non-users, matching by the NACC enrollment year}

To select the study baseline for non-users and to reduce the influence of
unmeasured confounding factors in our study, we used incidence density
sampling (IDS), which is often used in nested case-control studies within a
cohort.\textsuperscript{9,67} The IDS was to avoid different probability of drug initiation and non-
initiation among users and non-users. In our sampling procedure, we consider Z-
drug users as “cases” and non-users as “controls”. We randomly selected non-
users from participants who did not report hypnosedative use from the UDS initial visit to the year that they were selected as controls (study baseline). We matched the non-users to Z-drug new users with a ratio of 4:1 based on their year of UDS initial visit. Every time a participant reported Z-drug initiation, four controls were randomly selected (Figure 1b). The controls reported no hypnosedative intake from the initial UDS visit to the year of users’ initiation. Participants who reported Z-drug use later than the time they were selected as controls were still considered as non-users on the index date (study baseline) based on the IDS method. These late initiation Z-drug users were not on Z-drugs from the UDS initial visit to the time they were selected. However, they were not in the risk set at the visit after they were selected as controls.\textsuperscript{67,68} For example, if user A initiated Z-drug in 2011 but was randomly selected as a non-user control in 2009, user A will be treated as a non-user control for Z-drug users in 2009 and will not be selected as a user or non-user after year 2009.

\textit{Covariates and Potential Confounding}

In addition to the exposure of interest, we identified covariates for our study based on the literature and substantive knowledge.\textsuperscript{4,10,42,44-46} Initially considered covariates which were associated with both Z-drug use and cognitive impairment can be generally classified into five groups: genetic risk factors, demographic characteristics, behavioral risk factors, chronic clinical or mental conditions, and other medications. Genetic risk factors of Alzheimer’s Disease included APOE-\(\varepsilon4\).\textsuperscript{4} Demographic characteristics involved age, sex, education, and race.\textsuperscript{4,44} Behavioral risk factors included alcohol abuse, tobacco use, diet
and physical activity.\textsuperscript{42,44-46} We included chronic clinical or mental conditions such as BMI, cardiovascular diseases, diabetes, insomnia, sleep apnea, REM syndrome, depression, and anxiety in the analysis. We also considered other medications such as over the counter hypnosedatives (OTC) and antidepressants in the study.\textsuperscript{4,42,44-46,69}

\textit{Directed Acyclic Graph}

We created a directed acyclic graph (DAG) to identify the minimal sufficient adjustment sets for estimating the total effect of Z-drugs on cognition.\textsuperscript{70} Causal relationships between variables were based on previous literature.\textsuperscript{4,11,42,69,71,72} According to the specified DAG (Figure 2), the suggested minimal adjustment set included age, alcohol abuse, cardiovascular conditions, depression or anxiety, diabetes, diet or physical activity, education, over-the-counter hypnosedatives, parasomnia/REM syndrome, race, sex, sleep apnea, tobacco use, and unmeasured variables. Since the participants had different cognitive status at the study baseline and whether they were normal or not might influence the drug-outcome association, we also included the cognitive status at the study baseline in the DAG.\textsuperscript{2,29,44} The potential confounding factors for analysis were narrowed down based on data availability (i.e., whether the variables are measured in the NACC database). We included age, sex, race, antidepressant use, cardiovascular disorders represented by stroke, hypertension, and diabetes, alcohol abuse, tobacco use, and cognitive status (normal: yes versus no) at the study baseline as potential confounding factors for analysis.\textsuperscript{70}
Propensity Scores and Weighting

Covariates were determined at the study baseline, which was defined as the visit prior to drug initiation or the index visit for non-users based on the DAG. To further reduce the confounding effects in this study, we applied the propensity score (PS) method for measured confounders. A PS is the conditional probability of treatment or exposure (or corresponding non-treatment or non-exposure) given all measured confounders.73,74 Ideally, the probability of treatment is unrelated to confounders among participants with the same PS, like in a randomized trial but it may not be the case in most observational studies.73,74

We applied a logistic regression model to estimate the PS score for both comparisons: Z-drug users versus BZD-users and Z-drug users versus non-users. Covariates were selected based on the DAG, including age at study baseline, race, antidepressant use, education, alcohol use, stroke, hypertension, diabetes, tobacco use, and cognitive status at study baseline (Figure 2). The dependent variable for the logistic regression for PS estimation was the medication user group. The PS distributions by group are shown in Figures 3a and 3b. Treated (Z-drugs) and control (BZD-users or non-users) participants with similar PS values had similar covariate distributions and were comparable.61,73-76 PS matching is a common method to keep baseline characteristics between groups in balance.74 However, to avoid the reduced sample size by PS matching and to improve the precision, we adopted stabilized inverse probability of weighting (SIPTW) for our analysis.73,74,76
Unlike matching, weighting does not result in reduction of the original sample size.\textsuperscript{77} The purpose of weighting is to reweight the individuals within the original treated and control groups to create a so-called pseudo-population, in which there is no longer an association between the confounders and the probability of treatment.\textsuperscript{61,74,75} Two commonly used weighting schemes are IPTW and standardized mortality ratio weighting (SMRW).\textsuperscript{61,74,75} The SMRW uses the treated group as the standard population to reflect the proportion in the unadjusted treatment population.\textsuperscript{73,74,78} SMRW is calculated with value “1” in the treated and propensity odds in the untreated.\textsuperscript{78} The IPTW uses the total study group as the standard population.\textsuperscript{73,74,79} To calculate, IPTW is the inverse of the estimated PS (1/PS) for treated participants, and the inverse of one minus the estimated PS (1/(1-PS)) for control participants.\textsuperscript{61,74,75} Persons who receive an unexpected treatment are weighted up, while patients who receive expected treatment are weighted down.\textsuperscript{73,74} So the pseudo-population is, in theory, representative of the participant characteristics in the overall population from which the sample was drawn.\textsuperscript{73,74} Thus, IPTW results in estimates that are generalizable to the entire population from which the observed sample was taken; the estimated treatment effect is the population average treatment effect (ATE).\textsuperscript{73,74,79} IPTW can be particularly sensitive to the influence of patients who receive unexpected treatments.\textsuperscript{73,74} Precision of estimated effects could be improved by stabilizing the weights, by multiplying weights by the marginal probability of receiving treatment (in treated) and the marginal probability of not receiving treatment (in untreated).\textsuperscript{73,74}
Outcome and Measures

The outcomes of interest in the current study included neuropsychological test indicators and clinical indicators. Neuropsychological test indicators are changes in global cognitive function and executive function occurring one and two years after the index visit. Our outcomes for cognitive function included two measures of global cognitive status: the Mini-Mental State Examination (MMSE)\(^80\) and the Clinical Dementia Rating (CDR) sum of boxes scores.\(^81\) The MMSE is a widely used test of cognitive function among the elderly, which includes tests of orientation, attention, memory, language, and visual-spatial skills.\(^80\) MMSE ranges from 0-30, with lower scores indicating worse cognitive function.\(^65,80\) The commonly used single cutoff score of MMSE is 24, lower than which indicates abnormal cognition.\(^82\) The CDR sum of boxes is a global assessment of dementia severity, which is regularly used in clinical and research settings.\(^59,81\) The CDR sum of boxes scores range from 0.0 to 18.0, with 0.5 as the unit increment.\(^59,81\) The CDR sum of boxes staging categories include: 0 as normal, 0.5-4.0 as questionable cognitive impairment, 4.5-9.0 as mild dementia, 9.5-15.5 as moderate dementia, and 16.0-18.0 as severe dementia.\(^59,81\)

In addition, we also evaluated the association between Z-drug use and executive function change one and two years after Z-drug initiation. Executive function was measured by the Trail Making Tests (TMT) A (Trail A) and B (Trail B).\(^83-85\) The TMT is a measure of visual scanning, graphomotor speed, and executive function.\(^83\) The Trail A focuses more on visual search and motor speed skills, while the Trail B focuses more on executive control.\(^84-86\) On average, the
Trail A test score is 29 seconds, with more than 78 seconds indicating deficiency (maximum time allowed = 150 seconds).\textsuperscript{87-90} The Trail B test score is 75 seconds on average with more than 273 seconds as deficiency (maximum time allowed = 300 seconds).\textsuperscript{87-90}

For clinical indicators, we evaluated transitions in clinical cognitive status from study baseline to two years after drug initiation. Possible cognitive transitions included: normal to MCI, normal to dementia, and MCI to dementia. The MMSE, CDR sum of boxes, Trail A and Trail B scores were specified as continuous variables. The cognitive transition status was categorical.

**Statistical Analysis**

First, we conducted a descriptive analysis of the study population in three groups: Z-drug new users, BZD new users, and non-users. Second, we conducted regression analysis for the association between treatment methods and outcome variables. All regression models for our analysis used the SIPTW method.

*Model selection and goodness of fit*

Our primary outcome variables included two types: the continuous variables of neuropsychological tests including the MMSE, CDR sum of boxes, Trail A and Trail B tests, and the categorical cognitive transition variable as the clinical indicator. We applied the repeated measures general linear model for outcomes of the MMSE, CDR sum of boxes, and the Trail A and Trail B test scores with two repeating time points: one year and two years after drug initiation.
(two and three years after study baseline for non-users) respectively. We chose repeated measures to analyze the association between the continuous variables (the MMSE, CDR sum of boxes, Trail A, and Trail B test scores) and the exposure of interest due to the fact that the study contained repeated measures of the outcomes at two different time points (baseline and one or two years after initiation). In addition, the repeated linear models could allow us to evaluate the cognitive change influenced by both treatment methods and time.

For continuous outcome variables of neuropsychological tests, we compared R-squares between the repeated measure models and non-repeated linear regressions. We did linear regressions without repeated measures using the change of cognitive test scores as the dependent variables and treatment group as the independent variables. The R-squares of the linear regressions were smaller than the repeated general linear regressions (e.g., for MMSE, 0.0015 <0.0033). So the repeated measures were still the best of fit.

We used the Cox proportional hazards model to evaluate the effects of Z-drug use on time to cognitive transition in the two years following drug initiation. The cognitive transition was defined as cognitive change from normal to MCI, MCI to dementia, or normal to dementia from the study baseline to two years after the drug initiation. The cognitive transition in two years after drug initiation was: 25 among Z-drug users (11.4%), 35 among BZD-users (9.3%), and 105 among non-users (13.3%). The survival time of the participants were one year, two years, or censored if no cognitive transition at the end of two years after drug initiation.
The statistical significance level in our study was 0.05. We conducted all analyses using SAS 9.4® (SAS Institute, Inc., Cary, NC).

*Sensitivity Analyses*

For the neuropsychological tests measured by continuous variables, we performed a repeated general linear regression analysis for trajectories from baseline to the end of two years after drug initiation with three repeating time points—baseline, one year, and two years after drug initiation. For cognitive transitions, we did a sensitivity analysis comparing results from the Cox proportional hazards model with the Kaplan-Meier product-limit estimator. We conducted the Log-Rank test to estimate the difference of cognitive transitions between Z-drug users and their comparison groups.
CHAPTER 3

RESULTS

Study Baseline Characteristics

We selected participants from the NACC UDS dataset (September 2005-May 2017) according to the study’s inclusion and exclusion criteria. Based on the crude inclusion criteria that we provided for the NACC data request, 8,136 participants were initially included in the study population, among which 6,134 reported no hypnosedative use. After sample selection, we included 988 participants in our analysis. Among these participants, 219 were Z-drug new users, 376 were BZD new users, and 788 were non-users randomly selected from IDS and matched to Z-drug users based on their NACC enrollment year (1:4). In the IDS with matching, 197 out of the 219 Z-drug new users were matched to controls at the visits before they first reported the Z-drug initiation.

Participants’ characteristics at the study baseline (i.e., the visit before drug initiation) are shown in Table 1a. Some characteristics at baseline were similar in the comparison of Z-drug users and BZD-users with the following exceptions: BZD-users were approximately two years older than Z-drug users (P<0.0001), a 10% larger proportion of BZD-users were on antidepressants than those of Z-drug users (P=0.01), an approximately 7% smaller proportion of BZD-users did not have hypertension (P=0.01), and a 17% larger proportion of Z-drug users were more cognitively normal than BZD-users (P<0.0001). After the IDS and matching, most characteristics of Z-drug users and non-users were similar
without statistically significant difference, except that Z-drug users included more individuals who identified as White (P<0.05) and that a 10% larger proportion of antidepressant use than non-users (P<0.0001).

In addition, Table 1b showed arithmetic means of the cognitive test scores at study baseline, drug initiation, one year after drug initiation, and two years after drug initiation. The MMSE and the CDR sum of boxes were statistically different at baseline and at drug initiation between Z-drug new users and the BZD-users (P<0.05). All four cognitive test scores were statistically different between Z-drug users and the BZD-users at one year after initiation (P<0.05). The MMSE was statistically different between Z-drug new users and the BZD-users two years after initiation (P<0.05). Most test scores did not have statistically significant difference between Z-drug users and non-users except for the CDR sum of boxes at baseline (P<0.01).

**Z-drug Use and Change of Cognition and Executive Function**

**Z-drug new users versus BZD new users**

In this comparison of new users with the repeated measures of general linear regression, no statistically significant differences were found between Z-drug users and BZD-users (Table 2). However, statistically significant changes were found within user groups for the CDR sum of boxes and the Trail A test score change one year after Z-drug or BZD initiation (P<0.01), and for the CDR sum of boxes, and the Trail A and Trail B test scores two years after drug initiation (P<0.05). The CDR sum of boxes score was increased by 0.1 in Z-drug
users and by 0.2 in BZD-users one year after initiation. The Trail A test score was increased by 1.8 seconds in Z-drug users and by 2.7 seconds in BZD-users one year after initiation. These changes suggested potential cognitive decline and impairment of visual search and motor speed one year after initiation.83,84,87,88,92,93

For changes two years after hypnosedative initiation, the within-subject change of all four cognitive test scores was statistically significant (P<0.05). The CDR sum of boxes score was increased by 0.3 among both Z-drug users and BZD-users, indicating global cognitive impairment based on the CDR criteria.92 The Trail A test score increased by 3.6 seconds among Z-drug users and by 2.3 seconds among BZD-users, indicating a slowing down on the Trail A test. The Trail B test score increased by 8.6 seconds among Z-drug users and by 7.8 seconds among BZD-users, indicating a slowing down on the Trail B test.

To sum up the neuropsychological test results for Z-drug users and BZD-users: no statistically significant difference was found in the change between user groups. Both Z-drug users and BZD-users experienced global cognitive impairment and declines in visual search, motor speed, and executive control over the two years after drug initiation.

In addition, there was no statistically significant difference between two new user groups on hazards of cognitive transition two years after initiation (HR=1.49, 95%CI: 0.88-2.53) although Z-drug users had a 49% increased risk of cognitive transition over the two years after drug initiation than BZD-users.
Z-drug new users versus Non-users

In the comparison between Z-drug new users and the non-users, most of the outcome variables did not show statistically significant changes except the TMT test after Z-drug initiation between users and non-users. The difference of the change in the Trail B test score one year and two years after initiation (two years and three years after study baseline for non-users) was statistically significant between Z-drug users and non-users (P<0.05). Changes in cognitive tests over time within Z-drug users or non-users were also found for the CDR sum of boxes score (P<0.0001) and the Trail B test score (P<0.01) one year after initiation (two years after study baseline for non-users) and for all four test scores two years after initiation (three years after study baseline for non-users) (P<0.01).

The effect sizes for the statistically significant changes one year after initiation are as follows. The CDR sum of boxes increased by 0.1 for Z-drug users and 0.3 for non-users one year after initiation. The Trail B test score increased by 5.1 seconds for Z-drug users and 7.6 seconds for non-users one year after initiation. Regarding the between-group comparison, non-users had 2.5 seconds more decline in the Trail B test than Z-drug users. These changes indicated that both Z-drug users and non-users experienced increased global cognitive impairment regarding their CDR test and executive function decline regarding the Trail B test. However, Z-drug users had a slower decline in executive function one year after initiation than non-users.
Accordingly, the effect sizes for the statistically significant changes two years after initiation are listed below. The MMSE decreased by up to 0.3 points for users and 0.4 for non-users two years after initiation. The CDR sum of boxes increased by 0.3 for Z-drug users and 0.4 for non-users two years after initiation. The Trail A test score increased by 2.4 seconds for Z-drug users and 3.9 seconds for non-users two years after initiation. The Trail B test score further increased by 6.4 for Z-drug users and 12.5 for non-users two years after initiation. Accordingly, this difference in the Trail B test means that non-users slowed down by 6.1 seconds more than Z-drug users two years after drug initiation. Overall, the poorer MMSE and CDR scores over time indicated worse global cognitive function, and the slower the Trail A and B test scores indicated a decline in executive function. Z-drug users had a slower decline in executive function regarding Trail B test than non-users two years after initiation.

To sum up the change of neuropsychological tests one year and two years after initiation - Z-drug users had a slower decline in executive function regarding Trail B test over the two years after initiation. Both Z-drug users and non-users experienced global cognitive decline and decline in visual search, motor speed, and executive control over two years after drug initiation.

No statistically significant difference was found between Z-drug users and non-users on hazards of cognitive transition over two years after initiation (HR=0.89, 95%CI: 0.58-1.36) although Z-drug users had a 11% decreased risk of cognitive transition over the two years after drug initiation (three years after the study baseline) than non-users.
Interpretation of the results

With the SIPTW method for regression analysis, we could apply the results and conclusions of our study to the entire study population, which is the UDS participants who met the inclusion and exclusion criteria.\textsuperscript{74,75,79} The smallest clinically meaningful change of the MMSE reported by other studies was 1-2 points a year.\textsuperscript{94-98} Clinically meaningful change for the CDR sum of boxes is 0.5.\textsuperscript{59,92,99} The TMT cutoff points depend on age and education.\textsuperscript{88-90} Younger age and higher education are associated with a better Trail Making performance.\textsuperscript{88-90} Studies showed that a change of at least 1.5 times of standard deviations below the average in the Trail Making tests would show the cognitive decline.\textsuperscript{83,100} Accordingly, the effect size of our results, although some of them were statistically significant, may not show clinically meaningful changes. More studies are needed in the future to explore how the statistically significant difference of the TMT would relate to the clinically meaningful difference.\textsuperscript{83,100}

Sensitivity analyses

The repeated measures from baseline to the end of two years after drug initiation showed similar results as the repeated measures for one year and two years after drug initiation, respectively. The only difference was that the change of the Trail A test score was statistically significant between Z-drug users and non-users over the two years after drug initiation. Figure 4 and 5 showed the trajectories of the cognitive test score change over the two years.
For the comparison of Z-drug users and BZD-users in the MMSE test, there was a notably decrease in the MMSE test scores for BZD-users, indicating the cognitive decline within each individual over time. The MMSE test scores among Z-drug users increased from baseline to one year after initiation and then decreased since, indicating an improvement and a decline in cognitive function over the two years after initiation. However, none of these changes were statistically significant (P=0.15). Meanwhile, the two lines were almost parallel with each other, especially from one year to two years after drug initiation, indicating no difference in the MMSE change between the two treatment groups (P=0.30).

Similarly, the CDR sum of boxes scores increased over time within each individual, indicating more cognitive impairment over time (P<0.0001). However, the CDR score decreased from baseline to one year after initiation and increased since for Z-drug users, which made an overall change was similar to that for BZD-users, suggesting no difference in the change of the CDR sum of boxes test between Z-drug users and BZD-users over the two years after initiation.

Although the Trail A and Trail B test results showed a notable difference between Z-drug and BZD-users, the difference was not statistically significant between groups (P>0.05). There was a statistically significant change over time within each individual (P<0.001) for both the TMT test results, indicating a decline in executive control over time.
For the comparison of Z-drug users and non-users, although there was notable change between user groups, especially from baseline to one year after drug initiation for the MMSE and the CDR sum of boxes test scores, the change was not statistically significant (P>0.05, Table 3c). The MMSE test scores decreased significantly over time, suggesting cognitive decline within-subjects in both Z-drug users and non-users respectively. Similarly, the increased the CDR sum of boxes scores with a statistical significance over time, suggesting greater cognitive impairment over the two years after drug initiation.

The TMT test scores over the two years showed both between groups and within-subjects change (P<0.05). TMT times increased significantly (both the Trail A and B) over time, showing a slowing down of executing the tasks in TMT tests. However, the difference in the Trail A test score was not statistically significant for the analysis comparing baseline with two years after initiation. Taking the small effect size of 1.5 seconds into account, we would not consider it as a clinically meaningful change as the difference in the Trail B test between Z-drug users and non-users. In Figure 5, we could see an improvement of the Trail A test from baseline to one year after drug initiation and then a decline afterwards until the end of two years of initiation for the Z-drug users. The increase from baseline to one year may come from a practice effect or a real improvement.

To sum up, regarding the between-group comparison, both the repeated measures comparing baseline with one and two years after initiation and the three-time point trajectory analysis showed significant difference in executive
function among Z-drug users versus non-users. The executive function declined in both Z-drug users and non-users group but faster in the non-user group. This suggests that Z-drug users have a slower decline in executive functions than non-users among people 65 years and older in the US population.

Figure 6 showed the survival probability distributions. The Log-Rank test showed there was a statistically significant difference between the survival rates of Z-drug users and BZD-users (P<0.01), but no statistically significant difference between Z-drug users and non-users (P=0.25). The survival rate for both Z-drug users and non-users dropped to about 0.20 from one year after initiation, which means that a Z-drug user or a non-user has 80% risk of cognitive transition from one year after initiation. The survival rate dropped to 0.55 for BZD-users from one year after initiation and to less than 0.20 for Z-drug users. It means that a BZD-user has 45% risk of cognitive transition and a Z-drug user has approximately an 80% risk of cognitive transition from one year after initiation. This change of survival rate suggested a reduced risk of cognitive transition from normal to MCI, MCI to dementia or normal to dementia for BZD-users in comparison to Z-drug users in our study population. The significant difference between the survival of Z-drug users and BZD-users from the log-rank test did not completely agree with that from the Cox proportional hazards analysis. In the comparison of Z-drug users and non-users, both the Kaplan-Meier and the Cox analysis showed no statistically significant difference in the risk of cognitive transition. In the Cox regression analysis, Z-drug users showed a 21% lower risk of cognitive transition over two years after drug initiation without statistically
significant difference. However, the Kaplan-Meier showed Z-drug users had a slightly higher risk of cognitive transition from one year after drug initiation to two years. In the comparison of Z-drug users and BZD-users, both survival analyses showed no statistically significant difference either. However, the Cox regression suggested a 49% increased risk of cognitive transition among Z-drug users than BZD users without significance. The result from the Cox regression agreed with the Kaplan-Meier result, which showed about 50% increased risk of cognitive transition among Z-drug users than BZD-users. Further analysis with statistically significant results is needed to confirm if it was the limited sample size, the unbalanced baseline characteristics, or true that Z-drug users had an approximately 50% increased risk of cognitive transition than BZD-users over the two years after initiation.
In our study, all users and non-users had a decline in cognitive function, global cognitive impairment, visual scanning, graphomotor speed, and executive control. Regarding the between-group comparison, both the repeated measures with the two-time point and the three-time point trajectory analysis showed significant difference in executive function among Z-drug users versus non-users. Specifically, executive function declined in both Z-drug user and non-user groups but faster in the non-user group. This suggests that Z-drug users could have a slower impairment in executive functions than non-users among people 65 years and older in the US population. The Kaplan-Meier analysis showed BZD-users had a better survival rate from one year after drug initiation than Z-drug users. However, these results could be distorted by confounding by indication. For example, for the comparison of Z-drug users and non-users, if Z-drug users had better sleep quality, they may have a slower rate of decline in executive function.\textsuperscript{2,10} For the comparison of Z-drug users and BZD-users, it is possible that Z-drug users were prescribed with Z-drugs rather than BZDs because their major problem was insomnia rather than anxiety or other indications of BZDs.\textsuperscript{33,35} If insomnia is more likely to cause cognitive transition than other indications of BZDs, BZD-users would be more likely to have a better survival rate of cognitive transition.\textsuperscript{2,10,18,44,102}
However, our results rejected our hypothesis. Instead, Z-drug users showed a slower decline in executive function than non-users but a higher risk of cognitive transition than BZD-users in our study.\textsuperscript{53,63} It is difficult to compare our results to most other studies due to the study design and research question. For example, our study did not include the dose-response relationship or differentiate between Alzheimer’s and non-Alzheimer’s dementia.\textsuperscript{5} If the reduced number of GABA-A receptors in Alzheimer’s dementia mitigate the cognitive impairment from hypnosedatives as prior studies have reported, the significant effect for non-Alzheimer’s cognitive impairment could be attenuated or covered by the insignificant Alzheimer’s cognitive impairment.\textsuperscript{5,103} Meanwhile, not all studies have been specifically focused on Z-drugs or have similar measures of cognitive outcomes. Most studies about the hypnosedative use and its effects on cognitive impairment focused on BZDs or a combination of BZDs and Z-drugs, and furthermore, most studies also used dementia diagnosis as the cognitive outcome. The evidence of the association of Z-drugs and dementia is restricted to a few sub-analyses in BZD studies, suggesting a similar risk of dementia as seen with BZDs.\textsuperscript{44} Cheng et al. found that zolpidem users with a high cumulative dose in the first year after initiation had a significantly greater risk of Alzheimer’s disease than non-zolpidem users and low cumulative dose users.\textsuperscript{104} However, limitations existed in the study design, data collection, and generalization.

Limitations

Limitations of data collection
First, in a cohort study, the assignment of exposure and the non-exposure group should be based on the exposure status at baseline. However, our study used an existing dataset, which was not originally designed for our exposure and outcome of interest. Although we defined the exposure group based on the drug the participants first reported, differential misclassification could happen during follow-up when people switched drugs, stopped using the hypnosedatives which they were assigned to in the study, or provided unreliable information by self-reports. For example, 141 Z-drug users changed drug use status after they reported initiation of Z-drugs, among which 126 reported non-use of prescription hypnosedatives, 7 reported the use BZDs, and 8 reported the use of both Z-drugs and BZDs for their first change after Z-drug initiation during the UDS visit. Similarly, 192 BZD-users changed drug use status after they initiated BZDs, among which 183 reported non-use of prescription hypnosedatives, 3 reported the use of Z-drugs, and 6 reported the use of both prescription hypnosedatives for their first change after BZD-drug initiation.

Second, the dataset did not provide precise information for disease diagnoses including chronic sleep disorder and potential confounding comorbidities. For example, we did not have information on insomnia diagnoses, or that of any sleep disorder, or the indication of participants taking the hypnosedatives. We assumed that people who took hypnosedatives for at least one year would have chronic sleep disorders. Specifically, we used the hypnosedative prescription as a surrogate of the insomnia diagnosis. However, insomnia is not the only indication of prescription hypnosedatives. BZDs may
also be prescribed for other numerous indications including anxiety, muscle relaxation, relief from spasticity caused by central nervous system pathology, and epilepsy.\textsuperscript{24,25}

Apart from that, people with chronic sleep disorders may not report all hypnosedative usage during follow-ups or may not report the medication history accurately due to recall bias, self-report bias, and other information biases. For example, the hypnosedative information was self-reported by individuals about their drug intake within two weeks before each visit due to the requirements of the NACC cognitive tests. However, for our study, there could be information bias from self-reports and misclassification from lack of medication information beyond two weeks before each visit.

Third, information regarding initiation dates, termination dates, dose, and drug switching were unavailable as well. If cumulative dose plays an important role in the outcome-exposure association, our study may distort the association. For example, a subject reported Z-drug use at visit two and visit three so we assumed the subject was on the Z-drug for the entire year from visit two and visit three. However, the person may only take the drug for a few months during the year.

Additionally, there is a potential that Z-drugs may only influence short-term memories and cognitive functions as studies showed about the risk of falls and fractures. However, the UDS data did not provide information on the memory and
cognitive function test results the next few days after participants took hypnosedatives.

Limitations of generalization

Our study sample is unlikely to be representative of the target population. First, our study population had a higher socioeconomic status than the average older adults in a general population.\textsuperscript{105,106} The NACC population had a higher proportion of subjects with advanced education than the average older population.\textsuperscript{105,106} Second, the NACC data provided limited information on those non-White racial populations.\textsuperscript{105,106}

Important Methodological Improvement for Future Research

Despite these limitations, our study provided important methodology updates for future research on the association between hypnosedative use and cognitive impairment. Specifically, our study included different methods for confounding and bias reduction. First, we applied an ACNU design to reduce confounding by indication, healthy initiator, and healthy adherer bias. Second, we performed IDS to avoid putting the user groups at a disadvantage relative to the non-users in terms of time at risk.\textsuperscript{107} By matching the enrollment year while doing the IDS, we reduced the unmeasured confounding factors related to enrollment year. Third, we also conducted stabilized IPTW method based on PS to reduce the measured potential confounding factors for the drug-outcome association. The new user design that we performed allowed us to apply a repeated measure regression analysis to investigate the hypnosedative exposure and the cognitive
outcome. This analysis not only showed the change before and after drug initiation but also trajectories of cognitive change from baseline to one year and two years after drug initiation. Our sensitivity analysis gave us a better estimation by controlling uncertainties in analytic methods. In the future, if it is possible to link claims data to the NACC cohort, we can benefit from both databases. The NACC data could provide measures for cognitive tests. Additionally, claims data could provide additional clinical diagnoses, drug initiation and termination, and drug dose.

*Proposed Improvement of Study Design on the Study of Hypnosedatives and Cognitive Impairment*

A better study design with an improved data collection method is needed to avoid the above-mentioned limitations of investigating the association between prescription hypnosedatives and cognitive impairment. An appropriate study design will be more generalizable to the target population, and will make the results more applicable to public health and clinical practice. Here are the proposed study designs and evaluations of the designs regarding the study population, feasibility, potential biases, and ethical issues.

*A proposed study design - An observational study from a medical insurance cohort*

Regarding the ethical issues and feasibility of the clinical trials, we could also conduct a prospective cohort study with an ACNU design from a medical insurance claims data cohort. Similar to our current study, the ACNU design
will avoid confounding by indication, healthy initiator, and healthy adherer biases.\textsuperscript{9,60,61} Likewise, the index drug would be Z-drugs and the comparator BZDs.\textsuperscript{9} The Z-drug treatment group could be on any Z-drugs, and the BZD group could be on any BZD during the study. The improved ACNU design will allow us to reduce misclassification at exposure assignment and with disease diagnoses. The proposed study population would be older adults who are at least 65 years, have records in the selected database, and are diagnosed with insomnia based on ICD codes.

Possible information that we could obtain also includes prescriptive hypnosedative use (initiation and termination dates, dose, and drug names) and ICD codes of disease diagnoses such as insomnia, comorbidities, anxiety, depression, and other cognitive impairment.\textsuperscript{6,109} Then, we could conduct a retrospective cohort study with the prescriptive hypnosedative use as the exposure of interest for older adults with insomnia. The proposed follow-up time would be two years from drug initiation. The comparison group will be new Z-drug users and new BZD-users. Specifically, we will still apply the propensity score weighting methods to reduce potential confounding and to emulate a clinical trial design.\textsuperscript{61}

Analytically, this design will be more feasible with fewer ethical issues than the clinical trial - such as the ethical issues of intervention assignment and quality of life reduction during the washout period. However, more risks of misclassification and biases may occur. Misclassification would still occur during
follow-up due to the drug switch or missing information of over-the-counter hypnosedative use from self-report bias.

The medical insurance claims data provide better information for prescriptive hypnosedative use.\textsuperscript{110} This will improve the situation that the UDS dataset only offered the medication information two weeks before the visits by self-report. The claims data will also provide accurate information regarding clinical diagnoses of insomnia, other sleep disorders, and comorbidities, so we can have better control of the confounding variables.\textsuperscript{109,110} We could propose to explore medical insurance claims from both regular insurance companies and the Centers for Medicare and Medicaid Services (CMS).\textsuperscript{111} However, outcomes of interest may be difficult to collect since claims data do not include cognitive tests needed for our analysis.\textsuperscript{108,111} It is also possible that physicians have their preference of prescribing certain types of hypnosedatives. This preference may lead to channeling bias which may not be avoidable by the study based on the claims data.

To sum up, better designs could be developed but there will be no perfect designs for the research. Clinical trials to determine harmful effects are not ethical, and all observational data are limited. If the exposure is measured well, as in claims data, the outcomes of interest may not be measured as well. Appropriate study designs should be selected after evaluating the aims of the study, biases, and accuracy of the study results prediction, feasibility, and costs of the study, and ethical issues.
CHAPTER 5

IMPLICATIONS FOR PUBLIC HEALTH

Interestingly, both the cognitive outcome and the hypnosedatives exposure in our study are modifiable. In addition, prescription hypnosedative exposure is a modifiable factor regarding both patients’ and healthcare providers’ “behavior”: how patients take hypnosedatives and how clinicians prescribe hypnosedatives. Behavior change, in this sense, is a modifiable factor that has the potential to prevent health issues and improve the quality of life in a cost-efficient way. Furthermore, it draws attention to current public health research and practice. One of the aims of our study is to provide evidence of suggested prescription behavior change for healthcare providers and policy-makers and to improve the quality of life of the aging population in the US who are on prescription hypnosedatives. Also, the negative findings of the harmful effect from Z-drug prescriptions will provide implications to make adjustments for clinical and public health practice targeting the senior population through the collaboration of multiple-level - patients, healthcare providers, public health researchers and practitioners, and policy-makers.

How our study would help healthcare providers?

The healthcare system in the US is experiencing a significant transition regarding the focus and approaches to improve public health based on the change of population structure. According to the US Census Bureau, all baby boomers will be 65 years and older by 2030, and there will be 78.0 million people
older than age 65 by 2035 compared to 76.7 million who will be under 18 years old.\textsuperscript{115} The fast-growing aging population in the US requires adaptations in clinical practice now and in the near future due to the specific changes of physiology and heterogeneous health conditions of the elderly.\textsuperscript{116} However, current clinical practices and studies may not be sufficient to reflect the specific needs of the elderly.\textsuperscript{116} This mismatch has led to a lack of evidence-based medicine (EBM) in healthcare among the elderly regarding the elderly's physical and psychosocial situation, scientific evidence, and the physicians' expertise.\textsuperscript{116} Fundamentally, clinicians need to acknowledge that the changes of physical, mental, and social function of the elderly may lead to their increased vulnerability so that clinicians may need to create specific treatment goals and to conduct a thorough assessment based on the elderly's specific situation.\textsuperscript{116} In addition, clinical researches may need to modify study endpoints to target the senior population.\textsuperscript{116}

For cognitive impairment, a better understanding of the risk of prescription hypnosedatives could help with differential diagnoses of dementia for clinicians. Clinicians will be able to make prescriptions efficiently specific to the type of dementia, which will reduce costs and unnecessary medical treatment for patients and their caregivers.\textsuperscript{4} For example, if Z-drug users showed notably cognitive transition one year after drug initiation, clinicians may prescribe memantine to slow down the cognitive symptoms.\textsuperscript{117} However, this may associate with over-practice for clinicians if we have insufficient knowledge of dementia diagnosis. For instance, memantine may have side effects of body
aches, dizziness, constipation, and headache, which are risk factors of falls and will decrease the patients' quality of life. Also, dementia treatment medications are also prescribed for long-term use, which may lead to drug dependence for the patients. If the evidence that Z-drug has a higher risk of cognitive transition than BZDs is sufficient, clinicians are suggested to prescribe BZDs in patients with notable cognitive transition one year after Z-drug initiation. If seniors have multiple health conditions, an additional long-term medication prescription will also increase the interaction effects between drugs. For example, opioid analgesics may be co-prescribed with hypnosedatives by clinicians. Studies reported that more than 30% of overdoses involving opioids also involve BZDs. Combining opioids and hypnosedatives can be unsafe because both drugs are inhibitory to the central nervous system, which may sedate users and suppress breathing. The sedative effects of opioid and hypnosedatives can be the cause of overdose fatality, in addition to cognitive impairment. As a result, sufficient scientific evidence will allow clinicians make a better assessment and treatment plan tailored to the elderly’s specific medical needs.

How our study would help policy-makers?

For public health policy-makers, cost-effective policies and strategies are essential to prevent or postpone cognitive decline in the aging population and to improve the quality of life of seniors who are or will be on hypnosedatives. There is as of yet no cure for dementia, and dementia care is a financial and physical burden for patients, caregivers, and government agencies.
Regarding the changes of the elderly’s physical and psychosocial situation and heterogeneous health conditions, it is essential to modify and tailor current policies of clinical practice and research according to the specific needs of the aging population. First, policy-makers should present a list and order of suggested alternative hypnosedatives according to different health conditions so that clinicians can help patients to reduce medication interactions through their prescriptions. Second, policy-makers should design the electronic prescription system to allow clinicians to justify hypnosedatives types, doses, and frequency in the system for patients. Third, developing a peer comparison system through email lists is also essential so that clinicians can compare their hypnosedative prescribing rates with others and exchange feedbacks. Fourth, adding hypnosedative prescribing to the pay for performance system will be helpful to regulate clinicians’ prescription behaviors and to reduce over-practice more efficiently.

**How our study would help public health researchers and practitioners?**

Furthermore, to increase clinicians’ awareness of the special elements in aging-specific practice and the awareness of the seniors and their caregivers on improving their quality of life and preventing cognitive impairment, public health practitioners could develop an educational program for clinicians, patients, and their caregivers about hypnosedative application and risk of cognitive impairment among the elderly. For example, this educational program would emphasize the importance and benefits of the lifestyle intervention for the patients and their caregivers and using medical devices for sleep disorders before clinicians
prescribe hypnosedatives with cognitive risks.\textsuperscript{12,31,114} This educational program will also educate clinicians on how to prescribe hypnosedatives with caution and justification. Additionally, this program could be developed according to a community-based participatory research. For instance, a focus group with participants 65 years and older, their caregivers, and clinicians would have a panel discussion with public health practitioners and researchers about sleep disorders, interventions, and hypnosedative use.\textsuperscript{126,127} Then the public health team will identify priority issues regarding sleep disorders and intervention.\textsuperscript{126,127} Then a community-based research protocol of the education program would be developed based on the identified priority issues and implemented in communities.\textsuperscript{126} Periodical adjustments and feedback will be made by the public health team, and research findings will be disseminated and translated to the public and policy-makers.\textsuperscript{126}

**Conclusions**

The decreased MMSE, increased CDR summary score, and the increased the Trail A and Trail B test scores within user groups indicated that cognitive function declined over time among the UDS participants, whether or not they initiated hypnosedatives use. These changes indicated that regardless of hypnosedative usage, the cognitive function among the study population will decrease over time. The significant change in the Trail B test scores one year and two years after Z-drug initiation among Z-drug users compared to non-users suggested that Z-drug users had a slower decline in the Trail B test two years after drug initiation (three years after baseline for non-users). The Trail B test
score usually reflects executive function. Accordingly, we can infer that initiating Z-drugs could have a slower decline of executive function compared to non-users. However, there was no statistically significant difference between Z-drug users and BZD-users on the Trail B test. The insignificant results between Z-drug users and BZD-users could be due to the limited sample size and biases but could also indicate that there’s no difference in cognitive impairment between these two types of hypnosedatives.

So, clinicians may still be suggested to prescribe these drugs for possible indications to improve patients’ quality of life due to sleep disorders, anxiety, depression, and other related problems. However, the worse survival rates among Z-drug users compared to BZD-users at one year after initiation in the Kaplan-Meier analysis suggested that clinicians need to prescribe Z-drugs with caution for people with sleep disorders. Future studies with a better sample size and study design may explore if BZD-users are more capable in executive function than non-users. Studies with dose-response relationships are also essential to further investigate the effect of hypnosedatives use on cognitive impairment. With a better study design and data collection method, our study will be more beneficial to patients, clinicians, and public health policy-makers in the prevention of reversible dementia caused by hypnosedatives.
REFERENCES

16. Guarnieri B., Sorbi S. Sleep and cognitive decline: a strong bidirectional relationship: it is time for specific recommendations on routine assessment


42. Lader M. Benzodiazepine harm: how can it be reduced? *BJCP.* 2012;10(1111).


Table 1a. Participants' characteristics at study baseline, NACC, 2005-2017

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Z-drug vs. BZD-users</th>
<th>Z-drug vs. Non-users, the</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-drug users n=219</td>
<td>BZD-users n=376</td>
<td>P value</td>
<td>Z-drug users n=197</td>
</tr>
<tr>
<td>Age at baseline, y mean±SD</td>
<td>77.3±7.3</td>
<td>79.4±7.6</td>
<td>&lt;0.001*</td>
<td>77.0±7.3</td>
</tr>
<tr>
<td>Education, y mean±SD</td>
<td>15.8±3.0</td>
<td>15.8±5.4</td>
<td>0.94</td>
<td>15.6±3.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Male 77 (35.2)</td>
<td>117 (31.1)</td>
<td>67 (34.0)</td>
<td></td>
<td>268 (36.3)</td>
</tr>
<tr>
<td>Female 142 (64.8)</td>
<td>259 (68.9)</td>
<td>130 (66.0)</td>
<td></td>
<td>502 (63.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>White 195 (89.9)</td>
<td>324 (86.6)</td>
<td>175 (89.7)</td>
<td>654 (83.0)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Black 16 (7.4)</td>
<td>40 (10.7)</td>
<td>16 (8.2)</td>
<td>99 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Other 6 (2.8)</td>
<td>10 (2.7)</td>
<td>4 (2.1)</td>
<td>35 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Missing 2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant use</td>
<td></td>
<td></td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>No 169 (77.2)</td>
<td>253 (67.3)</td>
<td>152 (77.2)</td>
<td>667 (87.1)</td>
<td></td>
</tr>
<tr>
<td>Yes 50 (22.8)</td>
<td>123 (32.7)</td>
<td>45 (22.8)</td>
<td>99 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Missing 0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>Absent 89 (41.6)</td>
<td>111 (34.4)</td>
<td>79 (40.7)</td>
<td>335 (43.2)</td>
<td></td>
</tr>
<tr>
<td>Recent/active 122 (57.0)</td>
<td>196 (60.7)</td>
<td>113 (58.3)</td>
<td>415 (53.6)</td>
<td></td>
</tr>
<tr>
<td>Remote/inactive 3 (1.4)</td>
<td>16 (5.0)</td>
<td>2 (1.0)</td>
<td>25 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Missing 5</td>
<td>5</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>No 198 (90.4)</td>
<td>342 (91.0)</td>
<td>180 (91.4)</td>
<td>699 (91.3)</td>
<td></td>
</tr>
<tr>
<td>Yes 21 (9.6)</td>
<td>34 (9.0)</td>
<td>17 (8.6)</td>
<td>67 (8.8)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td></td>
<td></td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>No 105 (49.1)</td>
<td>146 (45.2)</td>
<td>95 (49.0)</td>
<td>394 (51.0)</td>
<td></td>
</tr>
<tr>
<td>Yes 109 (50.9)</td>
<td>177 (54.8)</td>
<td>99 (51.0)</td>
<td>379 (49.0)</td>
<td></td>
</tr>
<tr>
<td>Missing 5</td>
<td>53</td>
<td>3</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td></td>
<td></td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Absent 205 (95.8)</td>
<td>307 (95.1)</td>
<td>187 (96.4)</td>
<td>747 (96.0)</td>
<td></td>
</tr>
<tr>
<td>Recent/active 0</td>
<td>4 (0.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remote/inactive 9 (4.2)</td>
<td>16 (5.0)</td>
<td>7 (3.6)</td>
<td>27 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Missing 5</td>
<td>53</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Dementia diagnosis</td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
<td></td>
</tr>
<tr>
<td>Normal 197 (90.0)</td>
<td>276 (73.4)</td>
<td>178 (90.4)</td>
<td>714 (90.6)</td>
<td></td>
</tr>
<tr>
<td>Impaired-not-MCI 5 (2.3)</td>
<td>27 (7.2)</td>
<td>4 (2.0)</td>
<td>20 (2.5)</td>
<td></td>
</tr>
<tr>
<td>MCI 14 (6.4)</td>
<td>42 (11.2)</td>
<td>13 (6.6)</td>
<td>48 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Dementia 3 (1.4)</td>
<td>31 (8.2)</td>
<td>2 (1.0)</td>
<td>6 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>
Table 1b. Cognitive test means at baseline and during follow up, NACC, 2005-2017

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Z-drug vs. BZD-users</th>
<th>Z-drug vs. Non-users, the</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMSE mean±SD</td>
<td>MMSE mean±SD</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.7±1.7</td>
<td>28.0±3.2</td>
</tr>
<tr>
<td>Z-drug users</td>
<td>&lt;0.01*</td>
<td>Z-drug users n=219</td>
</tr>
<tr>
<td></td>
<td>0.3±0.8</td>
<td>1.0±2.8</td>
</tr>
<tr>
<td>BZD-users P value</td>
<td>0.001*</td>
<td>BZD-users n=376</td>
</tr>
<tr>
<td></td>
<td>36.6±17.6</td>
<td>39.8±22.0</td>
</tr>
<tr>
<td>CDR sum of boxes</td>
<td>mean±SD</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>100.9±58.0</td>
<td>112.3±68.9</td>
</tr>
<tr>
<td></td>
<td>mean±SD</td>
<td>0.05</td>
</tr>
<tr>
<td>Trail A</td>
<td>36.6±17.6</td>
<td>36.3±17.6</td>
</tr>
<tr>
<td>Trail B</td>
<td>100.9±58.0</td>
<td>98.4±55.5</td>
</tr>
<tr>
<td></td>
<td>0.001*</td>
<td>103.1±59.9</td>
</tr>
<tr>
<td></td>
<td>0.3±0.8</td>
<td>0.2±0.5</td>
</tr>
<tr>
<td></td>
<td>&lt;0.01*</td>
<td>Non-users n=197</td>
</tr>
<tr>
<td></td>
<td>36.6±17.6</td>
<td>36.8±17.4</td>
</tr>
<tr>
<td></td>
<td>100.9±58.0</td>
<td>98.4±55.5</td>
</tr>
<tr>
<td></td>
<td>0.001*</td>
<td>103.1±59.9</td>
</tr>
<tr>
<td></td>
<td>0.3±0.8</td>
<td>0.2±0.5</td>
</tr>
<tr>
<td></td>
<td>&lt;0.01*</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.7±1.9</td>
<td>28.0±3.2</td>
</tr>
<tr>
<td>Z-drug users</td>
<td>0.01*</td>
<td>Z-drug users n=219</td>
</tr>
<tr>
<td></td>
<td>0.3±0.8</td>
<td>1.0±2.8</td>
</tr>
<tr>
<td>BZD-users P value</td>
<td>0.001*</td>
<td>BZD-users n=376</td>
</tr>
<tr>
<td></td>
<td>36.6±16.5</td>
<td>39.8±22.0</td>
</tr>
<tr>
<td>CDR sum of boxes</td>
<td>mean±SD</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>103.1±60.0</td>
<td>112.2±68.9</td>
</tr>
<tr>
<td></td>
<td>mean±SD</td>
<td>0.12</td>
</tr>
<tr>
<td>Trail A</td>
<td>36.6±16.5</td>
<td>36.1±17.0</td>
</tr>
<tr>
<td>Trail B</td>
<td>103.1±60.0</td>
<td>99.8±56.9</td>
</tr>
<tr>
<td></td>
<td>0.01*</td>
<td>104.3±59.9</td>
</tr>
<tr>
<td></td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>One year after initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.7±1.9</td>
<td>28.2±2.3</td>
</tr>
<tr>
<td>Z-drug users</td>
<td>0.01*</td>
<td>Z-drug users n=219</td>
</tr>
<tr>
<td></td>
<td>0.3±0.9</td>
<td>0.6±1.9</td>
</tr>
<tr>
<td>BZD-users P value</td>
<td>&lt;0.05*</td>
<td>BZD-users n=376</td>
</tr>
<tr>
<td></td>
<td>36.0±17.4</td>
<td>41.1±21.5</td>
</tr>
<tr>
<td>CDR sum of boxes</td>
<td>mean±SD</td>
<td>0.01*</td>
</tr>
<tr>
<td></td>
<td>100.6±58.6</td>
<td>113.4±68.9</td>
</tr>
<tr>
<td></td>
<td>mean±SD</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Trail A</td>
<td>36.0±17.4</td>
<td>35.8±17.7</td>
</tr>
<tr>
<td>Trail B</td>
<td>100.6±58.6</td>
<td>99.4±59.0</td>
</tr>
<tr>
<td></td>
<td>0.01*</td>
<td>105.1±62.0</td>
</tr>
<tr>
<td></td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Two years after initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.6±2.0</td>
<td>28.1±2.1</td>
</tr>
<tr>
<td>Z-drug users</td>
<td>&lt;0.05*</td>
<td>Z-drug users n=219</td>
</tr>
<tr>
<td></td>
<td>0.5±1.7</td>
<td>0.7±1.7</td>
</tr>
<tr>
<td>BZD-users P value</td>
<td>0.18</td>
<td>BZD-users n=376</td>
</tr>
<tr>
<td></td>
<td>36.7±16.5</td>
<td>40.4±21.0</td>
</tr>
<tr>
<td>CDR sum of boxes</td>
<td>mean±SD</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>98.3±49.0</td>
<td>111.0±65.4</td>
</tr>
<tr>
<td></td>
<td>mean±SD</td>
<td>0.06</td>
</tr>
<tr>
<td>Trail A</td>
<td>36.7±16.5</td>
<td>36.2±16.8</td>
</tr>
<tr>
<td>Trail B</td>
<td>98.3±49.0</td>
<td>96.4±49.7</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>108.8±66.2</td>
</tr>
<tr>
<td></td>
<td>0.66</td>
<td></td>
</tr>
</tbody>
</table>
**Table 2a.** Z-drug effects on cognitive change, vs. BZD-users, one year after initiation

<table>
<thead>
<tr>
<th>Cognitive tests</th>
<th>Between subjects</th>
<th>Within subjects</th>
<th>Time and user interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Over one year</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>P=0.55</td>
<td>P=0.76</td>
<td>P=0.22</td>
</tr>
<tr>
<td>CDR sum of boxes score</td>
<td>P=0.81</td>
<td>P&lt;0.01*</td>
<td>P=0.25</td>
</tr>
<tr>
<td>Trail A test score</td>
<td>P=0.23</td>
<td>P&lt;0.01*</td>
<td>P=0.53</td>
</tr>
<tr>
<td>Trail B test score</td>
<td>P=0.74</td>
<td>P&gt;0.05</td>
<td>P=0.97</td>
</tr>
</tbody>
</table>

**Table 2b.** Z-drug effects on cognitive change, vs. BZD-users, two years after initiation

<table>
<thead>
<tr>
<th>Cognitive tests</th>
<th>Between subjects</th>
<th>Within subjects</th>
<th>Time and user interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Over two years</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>P=0.37</td>
<td>P=0.06</td>
<td>P=0.09</td>
</tr>
<tr>
<td>CDR sum of boxes score</td>
<td>P=0.57</td>
<td>P&lt;0.0001*</td>
<td>P=0.97</td>
</tr>
<tr>
<td>Trail A test score</td>
<td>P=0.29</td>
<td>P&lt;0.001*</td>
<td>P=0.42</td>
</tr>
<tr>
<td>Trail B test score</td>
<td>P=0.64</td>
<td>P&lt;0.001*</td>
<td>P=0.86</td>
</tr>
<tr>
<td>Cognitive transition</td>
<td>HR=1.49</td>
<td>P=0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI: 0.88-2.53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2c.** Z-drug effects on cognitive change, vs. BZD-users, one and two-year change trajectory

<table>
<thead>
<tr>
<th>Cognitive tests</th>
<th>Between subjects</th>
<th>Within subjects</th>
<th>Time and user interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Over two years</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>P=0.30</td>
<td>P=0.15</td>
<td>P=0.18</td>
</tr>
<tr>
<td>CDR sum of boxes score</td>
<td>P=0.66</td>
<td>P&lt;0.0001*</td>
<td>P=0.76</td>
</tr>
<tr>
<td>Trail A test score</td>
<td>P=0.12</td>
<td>P&lt;0.001*</td>
<td>P=0.20</td>
</tr>
<tr>
<td>Trail B test score</td>
<td>P=0.70</td>
<td>P&lt;0.001*</td>
<td>P=0.96</td>
</tr>
</tbody>
</table>
Table 3a. Z-drug effects on cognitive change, vs. non-users, one year after initiation

<table>
<thead>
<tr>
<th>Cognitive tests</th>
<th>Between subjects</th>
<th>Within subjects over one year</th>
<th>Time and user interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>P=0.20</td>
<td>P=0.08</td>
<td>P=0.20</td>
</tr>
<tr>
<td>CDR sum of boxes score</td>
<td>P=0.70</td>
<td>P&lt;0.0001*</td>
<td>P=0.11</td>
</tr>
<tr>
<td>Trail A test score</td>
<td>P=0.18</td>
<td>P=0.19</td>
<td>P=0.18</td>
</tr>
<tr>
<td>Trail B test score</td>
<td>P&lt;0.05*</td>
<td>P&lt;0.01*</td>
<td>P=0.56</td>
</tr>
</tbody>
</table>

Table 3b. Z-drug effects on cognitive change, vs. non-users, two years after initiation

<table>
<thead>
<tr>
<th>Cognitive tests</th>
<th>Between subjects</th>
<th>Within subjects over two years</th>
<th>Time and user interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>P=0.13</td>
<td>P&lt;0.01*</td>
<td>P=0.45</td>
</tr>
<tr>
<td>CDR sum of boxes score</td>
<td>P=0.89</td>
<td>P&lt;0.0001*</td>
<td>P=0.47</td>
</tr>
<tr>
<td>Trail A test score</td>
<td>P=0.07</td>
<td>P&lt;0.001*</td>
<td>P=0.35</td>
</tr>
<tr>
<td>Trail B test score</td>
<td>P&lt;0.01*</td>
<td>P&lt;0.001*</td>
<td>P=0.24</td>
</tr>
<tr>
<td>Cognitive transition</td>
<td>HR=0.89</td>
<td></td>
<td>P=0.58</td>
</tr>
<tr>
<td></td>
<td>95%CI: 0.58-1.36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3c. Z-drug effects on cognitive change, vs. non-users, one and two-year change trajectory

<table>
<thead>
<tr>
<th>Cognitive tests</th>
<th>Between subjects</th>
<th>Within subjects over two years</th>
<th>Time and user interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>P=0.18</td>
<td>P&lt;0.01*</td>
<td>P=0.69</td>
</tr>
<tr>
<td>CDR sum of boxes score</td>
<td>P=0.70</td>
<td>P&lt;0.0001*</td>
<td>P=0.47</td>
</tr>
<tr>
<td>Trail A test score</td>
<td>P=0.03*</td>
<td>P&lt;0.0001*</td>
<td>P=0.45</td>
</tr>
<tr>
<td>Trail B test score</td>
<td>P&lt;0.01*</td>
<td>P&lt;0.001*</td>
<td>P=0.43</td>
</tr>
</tbody>
</table>
Figure 1a. Study Scheme

NACC Enrollment Based on Original Criteria (Data requested from NACC)  
N=8136

>=Three visits

Eligible cohort for this study  
N=6134

Inclusion criteria for users:  
Users were defined to the group they firstly reported drug initiation after the NACC enrollment visit

Inclusion criteria for non-users:  
Reported no sleep aids use from NACC enrollment to the matched initiation visit;  
Randomly selected by the IDS procedure;  
Frequency matched to users with a ratio of Users:Non-users=1:4

Z-drug users  
N=219

BZD-drug users  
N=376

Randomly selected non-users  
N=788

Conducted SIPTW
Notes: User A enrolled in the NACC UDS visit in 2005 and reported Z-drug initiation in the UDS visit of 2006. We selected User A as a Z-drug new user starting from 2005 (study baseline) and with two follow-ups after Z-drug initiation until 2008. Control A1-A4 were randomly selected non-user controls for User A. Controls were randomly selected using the incidence density sampling procedure based on inclusion and exclusion criteria for non-users: did not report hypnosedative use from the UDS enrollment to the time of corresponding Z-drug user’s initiation (year of 2006); enrolled into the UDS in the same year as the corresponding Z-drug user (year of 2005). Noting that Control A2 actually initiated Z-drug use in 2008. However, Control A2 was still selected as a non-user control for User A based on the IDS method. The same criteria will be applied to select non-user controls for Z-drug users enrolled in the UDS and started initiation in other years (shown as User B and controls).
Figure 2. DAG for the association between Z-drug and cognitive impairment
Figure 3a. Propensity score distributions by treatment group, Z-drug users vs. BZD-users
Figure 3b. Propensity score distributions by treatment group, Z-drug users vs. non-users, IDS
Figure 4. Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. BZD-users

a. MMSE

![MMSE graph]

b. CDR sum of boxes

![CDR graph]
c. Trail Making Test-Trail A

![Trail Making Test-Trail A Graph]

---

d. Trail Making Test-Trail B

![Trail Making Test-Trail B Graph]
Figure 5. Repeated measures of cognitive test at baseline, one year, and two years after initiation, Z-drug users vs. Non-users

a. MMSE

b. CDR sum of boxes
c. Trail Making Test-Trail A

![Graph showing Trail A Mean over time with different groups: Treatment, Z-Drug user, Non-user.]

d. Trail Making Test-Trail B

![Graph showing Trail B Mean over time with different groups: Treatment, Z-Drug user, Non-user.]

Figure 6a. Kaplan-Meier Analysis Z-drug users vs. BZD-users
Figure 6b. Kaplan-Meier Analysis Z-drug users vs. Non-users