SLEEP PROBLEMS IN COMMUNITY-DWELLING OLDER ADULTS IN THE UNITED STATES

A DISSERTATION

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Dedication

To my father Võ Như Nam, mother Đinh Thị Sáu, SOS mother Nguyễn Thị Bảy and sister Võ Thị Thương

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Chapter 1: Overview: Background and Significance

1.1.Overarching sleep and health in older adults

The prevalence of sleep complaints or sleep disturbances is high among U.S. older adults, with approximately 60% of the population reporting sleep complaints including trouble with falling asleep, having to wake up at night, waking up too early and not being able to fall asleep again, feeling sleepy during the day and not feeling rested in the morning[1,2]. Consequences of not getting enough sleep and sleep disturbances include increased risk of fatigue[1], falls[1], accidents and vehicle crashes[3], lower work productivity[3], and worsened quality of life[1]. These consequences are exacerbated in older adults, who have a host of other medical conditions and functional impairments. For example, studies have shown that getting insufficient amount of sleep is associated with chronic diseases and conditions such as diabetes[4], cardiovascular diseases[5], depression[6,7] and obesity[8]. In addition, sleep disturbances have also been reported to be associated with functional impairments.[9]

Sleep health can be measured using 1) self-reported questionnaires such as the Pittsburgh Sleep Quality Index, the Karolinska Sleep Diary, the Sleep Timing Questionnaire and the Athens Insomnia Scale[10–12]; 2) overnight polysomnography (PSG) and 3) actigraphy. While self-reported questionnaires are the most practical and cost efficient method of collecting sleep data for large population-based studies, they may not be valid if subjective measures of self-reported sleep data are not the true measures of the actual sleep.[13] PSG has been used to assess sleep parameters and diagnose sleep apnea,

typically performed overnight at a sleep test center or hospital. While PSG has long been considered the gold standard method[14] to obtain detailed information on objectively measures of sleep-disordered breathing (SDB), disturbances of sleep architecture and wake and sleep time, PSG has its limitations[15] including: 1) sleep measures are only recorded for one night thus limiting the data necessary to assess patterns of sleep , 2) it requires highly trained staff and appropriate equipment and therefore is expensive to perform, and 3) it is inconvenient to patients or study participants to undergo overnight sleep test and 4) sleep during the PSG study may not be representative of usual sleep. Recently, with the developments and advances in technology, wrist actigraphy watches have become an alternative to PSG in sleep studies because they are more affordable than PSG equipment, more convenient to patients or study participants, and suitable for long term monitoring and collecting sleep-related data.

1.2.Sleep disordered breathing

Sleep-disordered breathing (SDB) or sleep apnea, a common disorder, is characterized by repeated pauses or reductions in breathing during sleep[16]. Treatments for SDB include the use of a continuous positive airway pressure (CPAP) machine, oral appliances therapy, surgery, and weight loss programs through exercise or by changing the position of the body while sleeping. According to the American Academy of Sleep Medicine (AASM), SDB was present in approximately 24.9 million U.S. adults (12%) in 2015. Of these 24.9 million, only 5.9 (23.7%) million U.S. adults have received a diagnosis of SDB. AASM has also estimated that the direct economic cost of undiagnosed SDB was approximately $149.6 billion in 2015, while costs for SDB treatments were estimated to be

only 33% of the costs for not diagnosing and treating sleep apnea. Among older adults, the prevalence of SDB is variable, ranging from 6-70% depending on which definition of SDB is being used and the populations being studied.[17–21] In older community dwelling men, the prevalence of SDB was estimated to be 25%.[17] Several risk factors have been shown to lead to the development and progression of SDB including overweight and obesity, increasing age, snoring, non-Caucasian race, sleepiness, male gender, smoking, alcohol use and large neck circumference.[17,22] Furthermore, SDB has been shown to be associated with prevalent and incident cardiovascular disease (CVD) including hypertension, coronary heart disease, cardiac conduction abnormalities, heart failure and stroke.[23–30] SDB is also associated with perioperative complications, motor vehicle accidents, cognitive impairment and cognitive decline.[22,31,32] Given that SDB is associated with adverse health outcomes, especially CVD events, SDB may be associated with higher healthcare costs and utilization across a variety of healthcare settings. If SDB is associated with higher subsequent healthcare costs and utilization, future intervention studies would be warranted to determine whether treatment of SDB lowers these measures of healthcare burden.

A number of studies, primarily in younger or middle-aged populations, have evaluated the association of SDB and healthcare utilization.[33–41] However, previous studies were limited by use of cross-sectional or case-control study designs [34–37,40] and inadequate control of potential confounders including body mass index (BMI).[33,41]One study used the modified Chronic Disease Score (CDS) as a proxy measure for healthcare utilization[41] and another study relied on administrative claims for the diagnosis of the obstructive sleep apnea (OSA).[39] Only three studies focused on older men and results were not consistent

between studies. [33,34,39] Given the higher prevalence of SDB in older men, there is a need for research evaluating the association of objective measures of SDB with subsequent total healthcare costs and utilization in community-dwelling older men.

1.3.Sleep efficiency

Sleep efficiency, defined as the percentage of time in bed spent sleeping, is a key measure of sleep health and has been shown to decrease with advancing age along with total sleep time, another important sleep parameter, defined as total hours per night spent sleeping while in bed.[42,42–44] Sleep efficiency can be assessed using self-reported questionnaires or objectively measured using actigraphy or polysomnography. While both short/long sleep duration and sleep efficiency below 70% have been shown to be predictive of increased mortality risk in older adults,[45,46] it has been proposed that sleep efficiency be the primary parameter to be examined and targeted to promote sleep health in older adults.[47] In addition, reduced sleep efficiency objectively measured by actigraphy is associated with impaired cognitive function and higher rates of cognitive decline in both older men[48] and women[49]. While some studies have examined sleep efficiency as a predictor of adverse health outcomes and conditions, there is a paucity of research that has considered sleep efficiency as an outcome measure. Recently, one study by Desjardins et. al examined factors associated with sleep efficiency among 2,468 community-dwelling Canadians (mean age = 73.7 [SD = 6.1 , range 65-96].[50] The study found that pain, nocturia, sleep medication use and awakening from bad dreams were all predictive of having a sleep efficiency below 80% among elderly people. These results are suggestive; however, this study was only cross-sectional and utilized interviews to assess self-reported efficiency

rather than objective measures. Given that reduced sleep efficiency is associated with increased mortality and cognitive impairment and decline, research is warranted to identify predictors of the development of incident reduced sleep efficiency in older adults. For example, the development of incident reduced sleep efficiency may be a cause, marker or consequence of developing adverse health conditions and diseases.

1.4.Significance and overview of proposed dissertation aim

To address current gaps in research presented above, the goals of the proposed study are to achieve the following expected outcomes: First, we will estimate the prevalence of sleep-disordered breathing and determine the association of SDB with subsequent measures of health care utilization and costs in U.S. community-dwelling older men. The findings will provide a clearer understanding of the impact of sleep-disordered breathing on healthcare costs and inpatient and post-acute care utilization, and possibly warrant future intervention studies that would have public health impact to determine whether treatment of sleep-disordered breathing lowers these measures of healthcare burden. Second, using standard logistic regression, we will examine and identify factors that are associated with incident reduced sleep efficiency in U.S. older community-dwelling men and women. The findings will provide insights on potential modifiable predictors of incident reduced sleep efficiency and guide design of future intervention studies. Third, we will use machine-learning methods through random forests to identify factors of importance in explaining incident reduced sleep efficiency in U.S. older community-dwelling men and women. Ultimately, this research proposal will improve our understanding of the determinants of the development of incident reduced sleep efficiency

in older men and women, and quantify the impact of sleep-disordered breathing on total healthcare costs and utilization in older men.

1.5.Specific Aims

Aim #1: To determine the association between objective measures of sleep-disordered breathing using polysomnography and subsequent healthcare costs and utilization in older community-dwelling men.

Hypotheses: Greater sleep-disordered breathing (as manifested by higher apnea-hypopnea index and higher oxygen desaturation index) among older men is associated with higher subsequent total health care costs, increased risk of hospital admission and greater length of inpatient stay, and increased risk of admission to a post-acute care skilled nursing facility

Aim #2: To identify risk factors for the development of incident reduced sleep efficiency (defined as sleep efficiency<70%) using polysomnography measures among older men aged 67 years and older with normal sleep efficiency (≥70%) at baseline.

Hypothesis: We hypothesize that incident reduced sleep efficiency among older men is associated with at least one of these risk factors. We will identify potentially modifiable characteristics that are independently associated with incident reduced sleep efficiency in older men. We will evaluate the following candidate risk factors: older age, nonwhite race, low educational level, low physical activity level, current or former smoker, alcohol intake ≥ 1 drink/day, higher caffeine intake, use of specific medications (antidepressants, benzodiazepines, sleep medications and other (nonbenzodiazepine)

sedatives/hypnotics), specific medical conditions and number of conditions (hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus), pre-frail and frail status, poorer self-reported health status, functional limitations (impairment in Instrumental Activities of Daily Living (IADL)), presence of depressive symptoms, presence of anxiety, having trouble sleeping due to pain, nocturia, bad dreams. All analyses will be adjusted for baseline sleep efficiency and study enrollment site.

Aim #3: To identify factors of importance in explaining incident reduced sleep efficiency in men aged 67 years and older using machine learning approaches via random forests.

Hypothesis: We hypothesize that specific medical conditions and number of conditions will be the most predictive variable with the highest variable importance score. The following variables will be candidate predictor variables: older age, nonwhite race, low educational level, low physical activity level, current or former smoker, alcohol intake ≥ 1 drink/day, higher caffeine intake, use of specific medications (antidepressants, benzodiazepines, sleep medications and other (nonbenzodiazepine) sedatives/hypnotics), specific medical conditions and number of conditions (hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus), pre-frail and frail status, poorer self-reported health status, functional limitations (impairment in Instrumental Activities of Daily Living (IADL)), presence of depressive symptoms,

presence of anxiety, having trouble sleeping due to pain, nocturia, bad dreams. We will determine the magnitude of variable importance in the random forest models.

Aim #4: To identify risk factors for the development of incident reduced sleep efficiency (defined as sleep efficiency<80%) using actigraphy measures among women in the 9th decade of life with normal sleep efficiency (≥80%) at baseline.

Hypothesis: We hypothesize that incident reduced sleep efficiency among older women is associated with at least one of these risk factors. We will identify potentially modifiable characteristics that are independently associated with incident reduced sleep efficiency in older women. We will evaluate the following candidate risk factors: older age, nonwhite race, low educational level, low physical activity level, current or former smoker, alcohol intake ≥ 1 drink/day, higher caffeine intake, use of specific medications (antidepressants, benzodiazepines, sleep medications and other (nonbenzodiazepine) sedatives/hypnotics), specific medical conditions and number of conditions (hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus), pre-frail and frail status, poorer self-reported health status, functional limitations (impairment in Instrumental Activities of Daily Living (IADL)), presence of depressive symptoms, presence of anxiety, having trouble sleeping due to pain, nocturia, bad dreams. All analyses will be adjusted for baseline sleep efficiency and study enrollment site.

Aim #5: To identify factors of importance in explaining incident reduced sleep efficiency in women in the 9th decade of life using machine learning approaches via random forests.

Hypothesis: We hypothesize that specific medical conditions and number of conditions will be the most predictive variable with the highest variable importance score. The following variables will be candidate predictor variables: older age, nonwhite race, low educational level, low physical activity level, current or former smoker, alcohol intake ≥ 1 drink/day, higher caffeine intake, use of specific medications (antidepressants, benzodiazepines, sleep medications and other (nonbenzodiazepine) sedatives/hypnotics), specific medical conditions and number of conditions (hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus), pre-frail and frail status, poorer self-reported health status, functional limitations (impairment in Instrumental Activities of Daily Living (IADL)), presence of depressive symptoms, presence of anxiety, having trouble sleeping due to pain, nocturia, bad dreams. We will determine the magnitude of variable importance in the random forest models. In order to address these aims, we will use data from 2 prospective cohort studies of older US community-dwelling adults (MrOS (men) and SOF (women)). Data from these two studies present a unique opportunity to address the above aims.

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Chapter 2: Study Designs, Data Collection and Methods

2.1.Data Source and Study Populations

2.1.1. The Osteoporotic Fractures in Men (MrOS) study

The prospective MrOS study recruited 5,994 men aged 65 and older from March 2000 through April 2002. The MrOS study population consists of community dwelling, ambulatory men, who were recruited from six clinical centers in the United States: Birmingham, Alabama; the Monongahela Valley near Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Palo Alto, California; San Diego, California; and Portland, Oregon. The objective of the study is to examine the determinants of fracture risk and other age-related conditions in older community-dwelling men i.e. lifestyle, medical and nutritional factors, bone mass and geometry, falls, strength and activity, anthropometric and neuromuscular measures; and to determine how factures affect quality of life in men. The inclusion criteria were: (1) ability to walk without the assistance of another, (2) absence of bilateral hip replacements, (3) ability to provide self-reported data, (4) residence near a clinical site for the duration of the study, (5) absence of a medical condition that (in the judgment of the investigator) would result in imminent death, and (6) ability to understand and sign an informed consent. To qualify as an enrollee, the participant had to provide written informed consent, complete the self-administered questionnaire (SAQ), attend the clinic visit, and complete at least the anthropometric, dual-energy x-ray absorptiometry (DEXA), and vertebral X-ray procedures. More details on the study design

and recruitment strategies of the MrOS study can be found elsewhere.[51,52] Following the baseline exam, additional interim visits and sub studies were completed every 1-2 years.

2.1.2. Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study

From December 2003 to March 2005, active MrOS participants were invited to participate in the ancillary Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. The overall aim of the MrOS sleep study was to investigate how sleep disorders affect health related outcomes in older men. To be eligible for the enrollment in the sleep study, participants had to report not sleeping with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) machines, not sleeping with a mouthpiece for snoring or sleep apnea in the past three months, not having an open tracheotomy, or not using oxygen therapy in the past three months during sleep. Exception was given if participant only used CPAP intermittently (< 2 times per week) and was willing not to wear the mask so the polysomnography (PSG) recording could be made. Of the 5,994 men in the initial MrOS cohort, 3135 (57%) agreed to participate in the Sleep Study (exceeding the recruitment goal of 3000 men).

2.1.3. Linkage of the MrOS cohort to Medicare Claims Files

Linkage of the MrOS cohort to Medicare Claims Files was completed in 2014, by submitting participant social security (SSN) and/or Medicare (HIC) numbers to the Centers for Medicare and Medicaid Services (CMS). In order for a linkage between MrOS cohort and Medicare claims files to be valid, SSN/HIC exact match was required; and information on date of birth (DOB), gender, date of death (if available) and last known residence (ZIP

code) from both MrOS cohort and Medicare claims files had to be in sufficient agreement with each other. MrOS enrollment began in 2000, and Medicare claims files were requested beginning 1/1/1999 in order to have a complete year of data available before the baseline MrOS visit. Medicare data was purchased from January 1999 to December 2016. Of the 5,994 men enrolled in MrOS, linkage to Medicare data was possible for 5,876(98%) of MrOS enrollees.

2.1.4. MrOS Sleep Visit 2

The second MrOS Sleep Visit (VS2) was completed between 11/10/2009 and 3/15/2012 at the six MrOS clinical centers: Birmingham, Alabama; the Monongahela Valley near Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Palo Alto, California; San Diego, California; and Portland, Oregon. All participants who remained active in the MrOS study and had usable polysomnography (PSG) and actigraphy data from the baseline MrOS Sleep Visit (VS) were eligible to be contacted to participate in the VS2. A special emphasis was put on minority recruitment for VS2, so all active minority participants with usable PSG and actigraphy data from VS were contacted for participation in VS2. Non-minority participants were contacted in random order for enrollment in VS2 until study recruitment goals were met. The overall study goal was to obtain usable PSG and actigraphy data on 1,000 participants at VS2. A total of 1055 participants were seen as part of VS2. 1044 have usable actigraphy data, and 1026 have usable PSG data. 1017 participants have both usuable actigraphy and usable PSG.

2.1.5. The Study of Osteoporotic Fractures in Women (SOF)

The Study of Osteoporotic Fractures (SOF) is a longitudinal epidemiologic study that was conducted to identify the risk factors for osteoporotic fractures in women. Women were recruited from four U.S. clinical centers (Baltimore, Maryland; Minneapolis, Minnesota; the Monongahela Valley nears Pittsburgh, Pennsylvania; and Portland, Oregon).[53] The SOF study enrolled 9,704 community-dwelling white women aged 65 years and older from 1986-1988. Women were excluded if they were unable to walk without assistance, or if they had undergone a previous bilateral hip replacement. Initially African American women were excluded from the study due to their low incidence of hip fractures, but from 1997-1998, 662 African American women aged 65 years and older were recruited.[54]

After completion of the baseline clinic visit, additional follow-up visits were conducted approximately every 1-4 years. This proposal will utilize actigraphy data from the Year 16 (or Visit 8) SOF exam that was conducted between 2002 and 2004; and Year 20 (or Visit 9).

2.2.Outcome Measures

2.2.1. Total healthcare costs

The primary outcome variable of interest in this study is the annualized total healthcare costs, which will be calculated using Medicare claims data as the sum of standardized inpatient hospital costs, Part A (an entitlement that provides inpatient coverage) paid skilled nursing facility (SNF) costs, outpatient costs, inpatient rehabilitation

facility (IRF) costs, and home healthcare costs. Costs for Part A paid SNF stays, for IRF stays, home healthcare and outpatient utilizations will be calculated using allowable charges for these services in the Medical Provider Analysis and Review (MedPAR) file. Standardized costs for hospital stays, SNF and IRF stays will be calculated using previously validated and published method. [1–3] All costs will be in U.S. dollars and adjusted for healthcare costs inflation to U.S. 2017 dollars. Total healthcare costs will be treated as a continuous variable in this proposal.

2.2.2. Incident reduced sleep efficiency

The second primary outcome variable of interest in this study is the incident reduced sleep efficiency. While sleep efficiency is a continuous variable, defined as the percent of time scored as sleep during the time in bed, incident reduced sleep efficiency will be treated as a dichotomous variable: not having incident reduced sleep efficiency at follow-up visit vs. having incident reduced sleep efficiency at follow-up visit. A man is considered to have no incident reduced normal sleep efficiency if he had normal sleep efficiency (sleep efficiency >= 80) at MrOS sleep visit and still had normal sleep efficiency (sleep efficiency >= 80) at MrOS sleep visit 2. Whereas, a man is considered to have incident reduced sleep efficiency if he had normal sleep efficiency (sleep efficiency >= 80) at MrOS sleep visit and had sleep efficiency < 80 at MrOS sleep visit 2. Likewise, a woman is considered to have no incident reduced normal sleep efficiency if she had normal sleep efficiency (sleep efficiency >= 80) at SOF visit 8 and still had normal sleep efficiency

(sleep efficiency >= 80) at SOF visit 9. Whereas, a woman is considered to have incident reduced normal sleep efficiency if she had normal sleep efficiency (sleep efficiency >= 80) at SOF visit 8 and had sleep efficiency < 80 at SOF visit 9. In MrOS, sleep efficiency measures were obtained from both in-home sleep studies using unattended polysomnography (Safiro, Compumedics, Inc., Melbourne, Australia) and the Octagonal Sleep Watch actigraphy, or SleepWatch-O, (Ambulatory Monitoring, Inc, Ardsley, NY). However, in this proposal, polysomnography sleep efficiency measures in MrOS men will be used because there was a change in the type of actigraphy watch utilized between the MrOS sleep visit 1 and the follow-up MrOS sleep visit 2. For women, however, actigraphy sleep efficiency measures will be used in this proposal.

2.2.3. Hospitalizations

2.2.3.1. All-cause hospitalizations

The first secondary outcome variable of interest in this study is all-cause hospitalizations during the three year follow-up period post MrOS sleep visit 1. All-cause hospitalizations will be treated as a dichotomous variable: no all-cause hospitalizations during the three-year follow-up post MrOS sleep visit vs. at least one all-cause hospitalization during the three-year follow-up period post MrOS sleep visit. Indicator of all-cause hospitalizations will be defined as having at least one acute short stay in the MedPar file.

2.2.3.2. Hospitalizations due to cardiovascular diseases (CVD)

Another secondary outcome variable of interest in this study is CVD hospitalizations. CVD hospitalizations will be treated as a dichotomous variable: not having CVD hospitalizations during the three year follow-up post MrOS sleep visit vs. having CVD hospitalizations during the three year follow-up post MrOS sleep visit. CVD hospitalizations will be identified using Medicare inpatient claims data. CVD will include coronary heart disease, congestive heart failure, myocardial infarction and cerebrovascular accident (stroke). The international Classification of Diseases, Ninth Revision (ICD-9-CM) will be used to identify these CVD events from claims data. A CVD-related hospitalization will be defined as a hospitalization with a primary or secondary discharge diagnosis of coronary heart disease (ICD-9-CM codes 414.xx), congestive heart failure (ICD-9-CM codes 398.91, 428.0), myocardial infarction (ICD-9-CM codes 410.xx, 412, 429.7x) and cerebrovascular accident (stroke) (ICD-9-CM codes 433.xx, 434.xx).

2.2.3.3 Length of stays

The third secondary outcome variable of interest in this study is length of hospital stays. The hospital stays variable will be determined from MedPar file and is defined as total days spent as an inpatient during the three-year follow-up post MrOS sleep visit. Length of hospital stays will be calculated using the difference between discharge date and admission date for inpatient service. If a discharge date is missing then length of hospital stays will be replaced by an already created length of stays in the Medpar file.

2.2.3.4 Admissions to post-acute skilled nursing facilities (SNF)

Admissions to the post-acute skilled nursing facilities will be used as another measure of healthcare utilization in this proposal. Admissions to post-acute SNF will be treated as a dichotomous outcome: not having admissions to post-acute SNF vs. having admissions to post-acute SNF in the three-year period post MrOS sleep visit. Status of having at least one admission to post-acute SNF will be identified from the MedPar file.

2.3.Independent Variables

2.3.1. Independent variables for Aim #1

2.3.1.1. Primary independent variables

The primary independent variables in this proposal are the apnea-hypopnea index (AHI) and oxygen desaturation index (ODI). They are measures of sleep-disordered breathing. AHI will be defined as the average number of apneas and hypopneas per hour of sleep. Apneas are defined as a complete or almost complete cessation of airflow for more than 10 seconds. Hypopneas are defined as a >30% reduction in amplitude of either respiratory effort or airflow for more than 10 seconds associated with an oxygen desaturation of ≥4%.[4]

Severity of sleep apnea will be treated as a categorical variable with three categories: normal if AHI < 5; mild if AHI is between 5 and 15; and moderate to severe sleep apnea if AHI is ≥15.[5]

ODI is the mean number of oxygen desaturation events (≥4% decrease in peripheral capillary oxygen saturation [SpO2]) per hour of sleep. ODI will be treated as a categorical

variable with four categories to indicate severity of ODI: normal if ODI ≤5; mild if 5 < ODI ≤ 10; moderate if 10 < ODI ≤ 15; and severe if ODI > 15.[6]

This proposal will also consider two other measures of sleep-disordered breathing: 1) percent of sleep time with SpO2 <90% [%TST<90] and 2) obstructive sleep apnea (OSA), which is calculated as the sum of obstructive apneas (excluding central apneas) plus hypopneas associated with a ≥4% desaturation. Similar to the primary measures of sleep-disordered breathing, %TST<90 and OSA will be treated as categorical variables to indicate severity of SDB. Severity of %TST<90 (also known as nocturnal hypoxemia) will be categorized as normal if %TST<90 is less than 1%; mild if %TST<90 is between 1% and 3.5%; and at least moderate if %TST<90 is at least 3.5%. OSA will have the same cutpoints as AHI i.e. normal if OSA < 5; mild if OSA is between 5 and 15; and moderate to severe sleep apnea if OSA is ≥15.

2.3.1.2. Other covariates for Aim #1

The potential confounders related to aim #1 based on previous studies[7–10] and availability in the data sets are as follows:

Socio-demographic characteristics:

These include age, race/ethnicity, education, and clinical sites. Age will be treated as a continuous variable and measured in years. Race/ethnicity will be treated as a dichotomous variable: Non-Hispanic White vs. Other. Education will be treated as a three level categorical variable: less than high school, high school and beyond high school. Clinical sites will be treated as a categorical variable to indicate six clinical study sites:

Birmingham, Alabama; the Monongahela Valley near Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Palo Alto, California; San Diego, California; and Portland, Oregon.

Body composition and health-related clinical characteristics:

These include body mass index, self-reported health status, smoking status, physician diagnosis of diabetes, hypertension, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases (CVD). CVD will be defined as having any of these self-reported conditions: coronary heart disease, stroke or congestive heart failure, where coronary heart disease is defined as having any of these conditions: angina, myocardial infarction, angioplasty, or coronary artery bypass. A participant is considered to have hypertension if he reported having hypertension or using anti-hypertensive medications or having systolic blood pressure ≥140 mmHg or having diastolic blood pressure ≥90 mmHg.[11] Body mass index will be calculated as weight in kilograms divided by the square of height in meters, and treated as a continuous variable. Self-reported health status will be treated as categorical variable with three categories: fair, poor or very poor, and good/excellent.

History of smoking status will be treated as categorical variable with three levels: never, past or current. History of having diabetes, hypertension, COPD and CVD will be treated as dichotomous variables: history of not having diabetes, hypertension, COPD or CVD vs. history of having these conditions.

2.3.2. Independent variables for Aims #2,3,4,5

The potential predictors of interest related to aim #2,3,4,5 based on previous studies [12,13] and availability in the data sets are as follows: age, race, educational level, physical activity level, history of smoking status, alcohol intake, caffeine intake, use of specific medications (antidepressants, benzodiazepines, sleep medications and other (nonbenzodiazepine) sedatives/hypnotics), specific medical conditions and number of conditions (hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus), pre-frail and frail status, poorer self-reported health status, functional limitations (impairment in Instrumental Activities of Daily Living (IADL)), depressive symptoms, anxiety, trouble sleeping due to pain, nocturia, bad dreams.

Demographic and lifestyle factors:

Age will be defined at age at MrOS sleep visit 1 for men and at SOF visit 8 for women. It will be treated as a continuous variable measured in years. Race/ethnicity for both men and women in MrOS and SOF will categorized as Non-Hispanic white vs. Others and treated as a 2 level categorical variable. Educational level will be defined as the highest education obtained and be expressed as a categorical variable with three levels: less than high school, high school, and college or more. Low physical activity will be defined using self-report of never walking for exercise and never engaging in vigorous activity (e.g. regular activity long enough to break a sweat). It will be treated as a dichotomous variable: low physical activity vs. normal physical activity. History of smoking will be self-reported and treated as a categorical variable with two categories: past/current vs. never. Alcohol

use (including beer, wine or mixed drinks) in the past 30 days will be self-reported and treated as a categorical variable with two categories: no alcoholic drinks in the past 30 days vs. at least 1 alcoholic drink in the past 30 days. The amount of caffeine intake will be treated as a continuous variable and measured in mg/day.

Use of medications:

Use of antidepressants, benzodiazepines, and other (non-benzodiazepine) sedatives/hypnotics will be self-reported and treated as categorical variables with two categories: current use of medications in a given medication class vs. non-user of medications in a given medication class.

Self-reported medical conditions:

Self-reported medical conditions will be categorical variable (present/absent) and include hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus. We will examinine multimorbidity (multiple medical conditions) as a predictor and express it as the sum of the medical conditions present (e.g. no condition, 1 condition, 2 condition, 3 or more conditions)

Frailty will be defined using the SOF index[14] and will be identified if data is available for at least two of the following three components of SOF frailty index: 1) indication of weight loss of ≥5% between SOF visit 6 (Year 10) and SOF visit 8(Year 16) for women and between MrOS baseline visit and first MrOS sleep visit for men, regardless of whether a woman/man was trying to lose weight or not; 2) indication of being unable to

stand up from a chair five times without using the arms; and 3) indication of having poor energy will be identified by an answer of "No" to the question "Do you feel full of energy?". A man/woman will be classified as having robust status if he/she has none of these three components, intermediate (pre-frail) status if he/she has 1 component, and frail status if he/she has at least 2 components. Thus frailty status will be treated as a categorical variable with 3 levels: robust vs. intermediate (pre-frail) vs. frail.

Overall health status will be self-reported and treated as a binary variable (excellent/good health vs. fair/poor/very poor health).

Impairment in Instrumental Activities of Daily Living (IADL) will be defined based on answers of yes/no to having difficulty of doing the following five activities: heavy housework, walking 2 to 3 blocks, climbing 10 stairs, shopping for groceries or clothing, and preparing meals on his/her own.[15,16] A person is considered to have an IADL impairment if they reported difficulty on at least one activity, and no IADL impairment is they responded no to all questions.

Mental and physical health:

The short form Geriatric Depression Scale (GDS-15), with values from 1 to 15, is a validated questionnaire[17–19] that has been widely used in the literature to measure depression disorder among older adults[20]. We will use a standard clinical cutoff, i.e. a person has depression if their GDS-15 score is at least 6.[19] Thus, depression will be defined as a categorical variable with two categories: having depression (GDS-15 score $\geq$6) vs. not having depression (GDS-15 score < 6). Anxiety level will be defined using the Goldberg

anxiety score [21] A person is considered to have significant anxiety symptoms if their Goldberg anxiety score is ≥5[21]. Thus anxiety will be treated as a categorical variable with two categories: significant anxiety symptom vs. not.

Sleep habits:

Trouble sleeping due to 1) pain, 2) nocturia, and 3) bad dreams will be self-reported and treated as three separate categorical variables. These variables will be based answers to questions "During the past month, how often have you had trouble sleeping because you have pain/nocturia/bad dreams?" The answers will be: 1) no trouble sleeping during the past month, 2) less than once a week, 2) once or twice a week, and 3) three or more times a week. A man/woman will be categorized as having no trouble sleeping during the past month due to pain/nocturia/bad dreams vs. at least some trouble sleeping due to pain/nocturia/bad dreams (combining less than once a week, once or twice a week, and three or more times a week).

Baseline sleep efficiency:

Baseline sleep efficiency will be defined as the percent of time scored as sleep during the time in bed and will be treated as a continuous variable.

Table 2.1: Study variable definition and operationalization

Variable	Definition	Operationalization
Outcome/Dependent variables		
Total healthcare costs	Sum of standardized inpatient hospital costs, Part A (an entitlement that provides inpatient coverage) paid skilled nursing facility (SNF) costs, outpatient costs, inpatient rehabilitation facility (IRF) costs, and home healthcare costs.	Continuous: Expressed in whole U.S. dollars, adjusted for 2017 healthcare costs.
Incident reduced sleep efficiency	A man is considered to have incident reduced normal sleep efficiency if he had normal sleep efficiency (sleep efficiency >= 80) at MrOS sleep visit and had sleep efficiency < 80 at MrOS sleep visit 2. A woman is considered to have incident reduced normal sleep efficiency if she had normal sleep efficiency (sleep efficiency >= 80) at SOF visit 8 and had sleep efficiency < 80 at SOF visit 9.	Categorical: 1: Having incident reduced sleep efficiency (sleep efficiency >=80) 0: Not having incident reduced sleep efficiency (sleep efficiency < 80) Sleep efficiency measures for MrOS men were calculated using polysomnography. Sleep efficiency measures for SOF women were recorded using actigraphy watches.
All-cause hospitalizations	Defined as having at least one acute short stay in the MedPar file.	Categorical: 1: Having all-cause hospitalizations in the three year follow-up post MrOS sleep visit 1 0: Not having all-cause hospitalizations in the three year follow-up post MrOS sleep visit 1

Hospitalizations due to cardiovascular diseases (CVD)	Defined as a hospitalization that had a primary or secondary discharge diagnosis of coronary heart disease (ICD-9 codes 414.xx), congestive heart failure (ICD-9 codes 398.91, 428.0), myocardial infarction (ICD-9 codes 410.xx, 412, 429.7x) and cerebrovascular accident (stroke) (ICD-9 codes 433.xx, 434.xx).	Categorical: 1: Having CVD hospitalizations in the three year follow-up post MrOS sleep visit 1 0: Not having CVD hospitalizations in the three year follow-up post MrOS sleep visit 1
Length of stays	Defined as total days spent as an inpatient during the three-year follow-up post MrOS sleep visit.	Continuous: Unit in days.
Admissions to post-acute skilled nursing facilities (SNF)	Defined as an indicator of having admissions to acute SNF in the three-year period post MrOS sleep visit. Identified from the MedPar file.	Categorical: 1: Having SNF admission 0: Nott having SNF admission
Independent variables		
Independent variables for Aim #1		
Age	Age in years at the time of MrOS sleep visit	Continuous: Unit in years
Race	Race and ethnicity of MrOS men	Categorical: 0: White 1: Non-white
Education	Highest education level obtained	Categorical: 0: Less than high school 1: High school

		2: Beyond high school
Clinic sites	Clinical visit sites where MrOS participants were	Categorical: 0: Birmingham, Alabama 1: Pittsburgh, Pennsylvania 2: Minneapolis, Minnesota 3: Palo Alto, California 3: San Diego, California 4: Portland, Oregon
Body mass index (BMI)	BMI of MrOS men defined as weight in kilograms (kg) divided by his height in meters squared	Continuous: Unit in kg/m^2
Self-reported health status	Health condition compared to others as perceived by men at MrOS sleep visit	Categorical: 0: Good/excellent 1: Fair 2: Poor/very poor
Smoking status	History of smoking status of MrOS men at the 1st MrOS sleep visit	Categorical: 0: Never smoked 1: Past smoker 2: Current smoker
Diabetes mellitus	Self-reported physician diagnosis of diabetes at the time of MrOS sleep visit based on question “Have you ever had diabetes?”	Categorical: 0: No 1: Yes
Hypertension	History of having hypertension based on question “have you ever had hypertension” or based on history of anti-hypertensive medications or based on having systolic blood pressure ≥140	Categorical: 0: No hypertension 1: Had hypertension

	mmHg or having diastolic blood pressure ≥90 mmHg	
Chronic obstructive pulmonary disease (COPD)	Self-reported history of having COPD based on question "Have you had COPD?"	Categorical: 0: No 1: Yes
Cardiovascular diseases (CVD)	History of having CVD defined as having any of these conditions: coronary heart disease, stroke or congestive heart failure	Categorical: 0: No CVD 1: Had CVD
Primary predictors for Aim#1		
Apnea-hypopnea index (AHI)	Defined as the average number of apneas and hypopneas per hour of sleep	Categorical: 0: Normal if AHI < 5; 1: Mild if AHI is between 5 and 15 2: Moderate to severe sleep apnea if AHI is ≥15
Oxygen desaturation index (ODI)	Defined as the mean number of oxygen desaturation events (≥4% decrease in peripheral capillary oxygen saturation [SpO2]) per hour of sleep	Categorical: 0: Normal if ODI ≤5 1: Mild if 5 < ODI ≤ 10 2: Moderate if 10 < ODI ≤ 15 3: Severe if ODI > 15
Secondary predictors for Aim #1		
Hypoxemia	Defined as the percent percent of sleep time with oxygen desaturation events <90%	Categorical: 0: Normal if ODI ≤5 1: Mild if 5 < ODI ≤ 10 2: Moderate if 10 < ODI ≤ 15 3: Severe if ODI > 15

Obstructive sleep apnea (OSA)	Defined as the sum of obstructive apneas (excluding central apneas) plus hypopneas associated with a ≥4% desaturation	Categorical: 0: Normal if OSA < 5; 1: Mild if OSA is between 5 and 15 2: Moderate to severe sleep apnea if OSA is ≥15
Independent variables for Aim #2,3,4,5		
Age	Defined as age in years for MrOS men at MrOS sleep visit 1 and age in years for SOF women at SOF visit 8	Continuous: Unit in years
Race	Race and ethnicity of MrOS men and SOF women	Categorical: 0: White 1: Non-white
Education	Highest education level obtained	Categorical: 0: Less than high school 1: High school 2: College or more
Low physical activity level	Defined using self-report of never walking for exercise and never engaging in vigorous activity (e.g. regular activity long enough to break a sweat).	Categorical: 0: Normal physical activity level 1: Low physical activity level
Smoking status	Defined as self-reported history of smoking status	Categorical: 0: Never smoked 1: Past/Current smoker
Alcohol intake	Defined as the number of alcoholic beverages in the past 30 days.	Categorical: 0: No alcoholic drinks in the past 30 days 1: At least 1 alcoholic drink in the past 30 days

caffeine intake	Defined as the amount of caffeine intake, measured in mg/day	Continuous: Unit in mg/day
Use of antidepressants	Defined as history of use of antidepressants based on question “Have you used antidepressants?”	Categorical: 0: No 1: Yes
Use of benzodiazepines	Defined as history of use of benzodiazepines based on question “Have you used benzodiazepines?”	Categorical: 0: No 1: Yes
Use of sleep medications	Defined as history of use of sleep medications based on question “Have you used sleep medications?”	Categorical: 0: No 1: Yes
Use of other (nonbenzodiazepine) sedatives/hypnotics	Defined as history of use of (nonbenzodiazepine) sedatives/hypnotics based on question “Have you used other (nonbenzodiazepine) sedatives/hypnotics?”	Categorical: 0: No 1: Yes
Hypertension	Self-reported physician diagnosis of hypertension at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had hypertension?”	Categorical: 0: No 1: Yes
Stroke	Self-reported physician diagnosis of stroke at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had stroke?”	Categorical: 0: No 1: Yes
Angina	Self-reported physician diagnosis of angina at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had angina?”	Categorical: 0: No 1: Yes

Myocardial infarction	Self-reported physician diagnosis of myocardial infarction at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had myocardial infarction?”	Categorical: 0: No 1: Yes
COPD	Self-reported physician diagnosis of COPD at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had COPD?”	Categorical: 0: No 1: Yes
Parkinson disease	Self-reported physician diagnosis of Parkinson disease at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had Parkinson disease?”	Categorical: 0: No 1: Yes
Cataracts	Self-reported physician diagnosis of cataracts at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had cataracts?”	Categorical: 0: No 1: Yes
Rheumatoid arthritis	Self-reported physician diagnosis of rheumatoid arthritis at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had rheumatoid arthritis?”	Categorical: 0: No 1: Yes
Osteoarthritis	Self-reported physician diagnosis of osteoarthritis at the time of MrOS sleep visit or SOF visit 8 based on question “Have you ever had osteoarthritis?”	Categorical: 0: No 1: Yes

Diabetes mellitus	Self-reported physician diagnosis of diabetes mellitus at the time of MrOS sleep visit or SOF visit 8 based on question "Have you ever had diabetes mellitus?"	Categorical: 0: No 1: Yes
Frailty	Defined using SOF Frailty index[71] using: 1) weight loss of > 5% between SOF visit 6 (Year 10) and SOF visit 8(Year 16) for SOF and between MrOS baseline visit and first MrOS sleep visit for MrOS, regardless of whether a woman/man was trying to lose weight or not; 2) indication of being unable to stand up from a chair five times without using the arms; and 3) indication of having poor energy	Categorical: 0: Robust for having 0 components 1: Pre-frail for having 1 component 2: Frail for having at least 2 components
Self-reported health status	Health condition compared to others as perceived by men at MrOS sleep visit and by SOF women at SOF visit 8	Categorical: 0: Good/excellent 2: Fair/Poor/very poor
Instrumental Activities of Daily Living(IADL)	Defined by sum of scores of yes/no to having difficulty of doing the following five activities: heavy housework, walking 2 to 3 blocks, climbing 10 stairs, shopping for groceries or clothing, and preparing meals on his/her own	Categorical: 0: No IADL impairment if score of IADL = 0 1: Having IADL Impairment if score of IADL >= 1
Depression	Depression is defined using the Geriatric Depression Scale (GDS) from 1 to 15. A man/woman with GDS-15 score of at least is considered to have depression.	Categorical: 0: No depression if GGS-15 score < 6 1: Having depression if GDS-15score ≥ 5

Anxiety	Anxiety level will be defined using the Goldberg anxiety score with the highest score of 9.	Categorical: 0: No anxiety if Goldberg anxiety score < 5 1: Having anxiety if Goldberg anxiety score ≥5
Trouble sleeping due to pain	Defined as history of trouble sleeping due to pain	Categorical: 0: No 1: Yes
Trouble sleeping due to nocturia	Defined as history of trouble sleeping due to nocturia	Categorical: 0: No 1: Yes
Trouble sleeping due to bad dreams	Defined as history of trouble sleeping due to bad dreams	Categorical: 0: No 1: Yes
Baseline sleep efficiency	Defined as the percent of time scored as sleep as a fraction of total time in bed	Continuous: No unit

2.4.Analytical Plans

2.4.1. Proposed analytical plans for Aim #1:

Descriptive statistics including means, standard deviations, medians, interquartile ranges and correlations for continuous variables and frequency distributions consisting of numbers and percentages for categorical variables will be used to summarize the descriptive information of the outcome and independent variables.

Analysis of variance (ANOVA) will be used to examine relationships between SDB measures and characteristics at baseline sleep visit when these characteristics are continuous and normally distributed variables. For continuous variables at baseline sleep visit, whose distributions are skewed (median < mean), non-parametric Kruskal-Wallis tests will be used.

Chi-square or Fisher's exact tests will be used to examine relationships between SDB measures and characteristics of men at the baseline sleep visit that are categorical variables.

Multivariable regression models will be used to examine the associations of annualized total healthcare costs, outpatient costs, all-cause hospitalizations, CVD hospitalizations, admissions to SNF's, and length of stay with SDB measures. Specifically, generalized linear models (GLMs) with log link and gamma distribution, based on the preliminary results of the Modified Park[23] and Pregibon link[24] tests to account for highly right-skewed distributions of total healthcare and outpatient costs, will be utilized to

examine the associations between annualized total healthcare costs, outpatient costs and SDB. Multivariable logistic regression models will be used to look at the relationships between all-cause hospitalizations, CVD hospitalizations, admissions to SNF's with SDB. Two-part Hurdle models[25] will be employed to examine the relationships between length of stay in post-acute facilities and SDB.

Analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) or Stata, version 14 (StataCorp LLC, College Station, Texas). All significance levels reported will be two-sided with p-value < 0.05 for significance.

Generalized linear models (GLMs) to model total healthcare and outpatient costs data:

It has been shown that healthcare costs data are highly right-skewed due to the disproportionally high costs of few patients with severe medical conditions relative to the majority of patients.[26,27] Thus describing the distributions of healthcare costs data using standard approaches and appropriately choosing the right modelling techniques for these highly right-skewed healthcare costs data can be challenging .[26] The traditional general linear models require that the distributions of the residuals be normally distributed and that the residuals have equal variance (also known as homoscedasticity). However, these two assumptions will be violated when modelling healthcare costs data due to two reasons: 1) healthcare costs data is not normally distributed and 2) variance is not constant (violating homoscedasticity assumption), and has been shown to be directly proportional the square root of the mean healthcare costs.[27] A few non-parametric methods, for example smearing,

have been developed by Duan et al to address problems with modelling highly right-skewed healthcare costs data.[28] However, very few nonparametric methods can be used to examine the impact of covariates on healthcare costs.[29] The most commonly used method to deal with healthcare costs data is by first transforming healthcare costs data to log scale, and then using ordinary least square (OLS) regression[30] to estimate the effects of covariates on healthcare costs, then finally exponentiating the parameter estimates to get the values on the original dollar scale. However, log-transforming healthcare costs dollars then re-transforming parameter estimates to get to the exact dollar value can result in biased-estimates of the effects of independent variables on the original healthcare costs dollar.[23]

The generalized linear models (GLMs) are an extension of the general linear model.[31] GLMs are characterized by three components: 1) the linear predictor $\eta_i = \beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p$; where $\beta_0, \ldots, \beta_p$ are the regression coefficients; $x_1, \ldots, x_p$ represent a list of covariates; 2) a link function that describes the mean of the continuous outcome variable of interest, $E(Y_i) = \mu_i$, depends on the linear predictor: $g(\mu_i) = \eta_i$; and 3) a variance function that describes the variance, $var(Y_i)$ depends on the mean: $var(Y_i) = \phi V(\mu_i)$; where ϕ is the dispersion parameter and is a constant. In GLMs, the dependent variable Y_i, is assumed to be independently distributed, and in this proposal Y_i is total healthcare or outpatient costs. However, Y_i does not need to be normally distributed as in general linear model, and is assumed to follow an exponential family (including binomial, normal (Gaussian), multinomial, Poisson, etc). Some attractive features of GLMs include their ability to deal with continuous outcome variables whose variance is a function of the mean, and their elimination of back transformation of the model parameter estimates.[26] Thus GLMs have

been proposed to be the solutions to modelling healthcare costs data due to these appealing features. Importantly, the incorporation of Gamma distribution and log link function into GLMs to facilitate in interpreting parameter estimates[26,32] accommodates the skewness nature of healthcare costs data.

The Modified Park[32] test will be used to determine the relationship between raw-scale mean and variance functions in order choose the correct exponential family in GLMs. The Pregibon link test will be used to choose the correct link function. Preliminary data suggests that total healthcare and outpatient costs will be modelled using an exponential family of gamma distribution with log link.

Multivariate Logistic Regression:

The other outcomes of Aim#1 include binary dependent variables (yes/no): all-cause hospitalizations, CVD hospitalizations, admissions to SNF's. Thus multivariable logistic regression will be used to model the probability of these events occurring in this proposal. Logistic regression is a special case of GLMs and it models to log odds of the event happening as a linear combination of one or more independent variables.[33] In the context of GLMs, 1) the distribution of the dependent variable Y_i follows a binomial distribution *Binomial* (n, π_i), where n is the total number of observations and π_i is the probability of having the event happening i.e. all-cause hospitalizations, CVD hospitalizations, admissions to SNF's, 2) the linear predictor $\eta_i = \beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p$; where $\beta_0, \ldots, \beta_p$ are the regression coefficients; $x_1, \ldots, x_p$ represent a list of covariates; and 3) the logit link function $\eta = log\left(\frac{\pi}{1-\pi}\right) = logit(\pi)$

Hurdle Regression to model length of stay:

Length of stay in post-acute care facilities is an indicator of recovery time for a patient treated for a condition in the hospital. It can also be considered as a measure of healthcare resource consumption and of hospital performance.[34] Length of stay in post-acute care facilities measured in days is considered to be count data that is characterized by having a significantly large proportion of zeros, high variability and over-dispersion in the data. Thus dealing with count data with these characteristics poses significant modelling challenges. There are a few modelling techniques for count data: Poisson model, Negative Binomial model, Zero-Inflated model, and Hurdle model. Poisson has been the most commonly used method to deal with count data, however, when dealing with length of stay, the assumption that the variance is equal to the mean in Poisson model will be violated. Thus using the Poisson model to model length of stay will not account for heterogeneity in the data due to the presence of significant over-dispersion in the data.[35,36] Negative binomial models are also unable to deal with heterogeneity in count data.[36] In this proposal, Hurdle logit-Poisson model (also known as two-part model), originally developed by Mullahy[37] will be used to estimate the length of stay in post-acute care facilities by categories of SDB and compare the length of stay between difference SDB categories through the use of rate ratios of days, as it performs as well as zero-inflated model, but it's simpler to use and has appealing interpretation.[36]

The Hurdle logit-Poisson is the most commonly used of the Hurdle regression. The Hurdle logit-Poisson model is a two-part model because it creates two models sequentially: 1) the Logit regression to model zero vs. non-zero counts i.e. the odds of getting

hospitalized vs. non-hospitalized in this proposal, and 2) a truncated Poisson regression to model non-zero outcomes i.e. number of days spent in in hospitals if hospitalized. The probability density function of the Hurdle logit-Poisson regression is as follows:

$$f(Y_i|X_i) = \begin{cases} \theta_i \; for \; Y_i = 0 \\ \dfrac{(1-\theta_i)e^{(-u_i)}u_i^{Y_i}}{(1-e^{(-u_i)})Y!_i} \; for \; Y_i > 0, where \; \theta_i = P(Y_i = 0) and \; u_i = \; e^{(X_i\beta)} \end{cases}$$

Due to the use of truncated Poisson regression in the second part of the Hurdle logit-Poisson model, bootstrapping will be done to obtain confidence intervals for analyses involving days spent in post-acute care facilities among those hospitalized. Bootstrapping is a method where data sets will be created via sampling with replacement, 1000 times, to create 1000 new data sets of the same size. The purpose of bootstrapping in the analyses is to deal with additional heterogeneity in the data.

The Hurdle logit-Poisson model will be run using Proc NLMIXED, SAS version 9.4 (SAS Institute Inc., Cary, NC).

2.4.2. Proposed analytical plans for Aims #2,4:

Descriptive statistics including means, standard deviations, medians, interquartile ranges and correlations for continuous variables and frequency distributions consisting of numbers and percentages for categorical variables will be used to summarize the descriptive information of the outcome and independent variables.

Chi-square or Fisher's exact tests will be used to examine if there is any difference in categorical variables by status of incident reduced sleep efficiency. T-test will be used to test for difference in means of continuous variables by status of incident reduced sleep

efficiency if the continuous variables are normally distributed. In the case of skewed continuous independent variables, non-parametric Wilcoxon rank-sum test will be used.

The outcomes of Aims #2 and #4 include binary dependent variables (yes/no): incident reduced sleep efficiency (defined as sleep efficiency<80%) using polysomnography measures among older men aged 67 years and older and incident reduced sleep efficiency (defined as sleep efficiency<80%) using actigraphy measures among women in the 9th decade of life. Thus multivariable logistic regression will be used to model the probability of these events occurring in this proposal. More details on multivariate logistic regression are described above. Base models will be adjusted for age and site. Each individual potential predictor will then be added to the base model separately to examine the age- and site-adjusted associations between the odds of developing incident reduced sleep efficiency and the potential predictor. The final multivariable models will include age, site and potential predictors, whose p-values in the age- and site-adjusted models are less than <0.10. All models will be adjusted for sleep efficiency at MrOS sleep visit 1 (for men) and SOF visit 8 (for women) as a continuous variable in order to make sure that any significant associations between incident reduced sleep efficiency and potential covariates are independent of the variability in baseline sleep efficiency.

All analyses in Aims #2 and #4 will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC)

2.4.3. Proposed analytical plans for Aims #3,5:

Random Forests:

In Aims#4 and #5, random forests will be used to identify independent variables that are most predictive of incident reduced sleep efficiency in men and women. The results will be compared to those obtained from the traditional logistic regression models in Aims #2,3 for classification problems involving binary outcomes.

Random forest technique originally proposed by Breiman (2001)[38] is a supervised machine learning technique and is an extension of Classification and Regression Trees (CART).[39] Random forests are ensembles of decision trees that are trained using bootstrapped samples randomly selected from the original dataset to identify and rank most important/predictive features/characteristics that are classifiers of an outcome through the use of variable importance measures (VIM).[38] The use of building decision trees and then aggregating these trees to cast a vote for the predicted outcome of interest given a list of features/independent variables leads to decorrelation between individual tree predictions and reduces the variance compared to using single decision trees.[40] The advantages of random forests include 1) its ability to deal with both small sample sizes and data with complex data structures i.e. high dimension data, where number of predictors/features is higher than the number of observations in the data sets, 2) its robustness to noise i.e. variability in the data sets, 3) its ability to deal with non-linear data and missing data, and 4) less amount of tuning of hyper-parameters. As a result, random forest algorithm has been applied to many fields such computational biology, personalized medicine and engineering, etc. and has been proven to perform better and produce higher accuracy than other classification algorithms.[41–46] There are three processes that are fundamental to random forest technique: 1) use of two types of randomness: a) each tree is constructed

using a randomly bootstrapped sample of the training data (two-thirds of the original data, also known as learning data) , b) a random sample of predictors among all potential predictors are considered to be potential splitting variables or nodes (usually taken as a square root of the number of predictors for classification and number of predictors divided by three for regression), 2) bagging: a process where predictions from bootstrapped samples (sample with replacement from the training dataset) are aggregated and averaged to come up with the final prediction; and 3) cross-validation – a method that is used to evaluate how well the random forest models from training data apply to the data that were not used to generate those results. The data that is not used to create the random forest models are called out-of-bag (OOB) data (also considered as validation/test data), which is one-third of the original data.

In Aims #4 and 5, predictive random forest models will be obtained to identify predictors most predictive of incident reduced sleep efficiency in men and women using a set of 29 potential predictors. The data sets in Aims#4 and 5 will first be divided into two parts: training data sets (two-thirds of the original data) and validation data sets (OOB data) (one-third of the original data) based on Breiman (2001).[38] Then to create random forest models for prediction of incident reduced sleep efficiency in each aim, the following steps will be carried out in this proposal:

1) With replacement, create 500 bootstrapped samples of training data set. These 500 samples have the same size as the training set. The use of 500 bootstrapped samples to create 500 trees as a hyperparameter in random forest models is the default and has been shown to produce reliable and stable results in many practical applications.[47]

2) Then generate 500 independent trees from these 500 bootstrapped samples without pruning by randomly selecting a subset of 5 predictors at each node (approximately square root of 29 potential predictors) to be considered as potential splitting variables.

3) Evaluate the importance of each variable using the OOB data by running the OOB data through the 500 trees generated in step 2. Variable importance for each of the 29 potential predictors in predicting incident reduced sleep efficiency is calculated as the difference between prediction error (also known as impurity) when the variable in the OBB is randomly permuted while the other variables remain the same. An average value of variable importance score for each potential predictor will be calculated for the 500 trees and then used to rank and determine which predictor is most predictive of incident reduced sleep efficiency in men and women in Aims #4 and 5.

The accuracy and performance of random forest models in Aims#4 and 5 will be evaluated using the out-of-bag (OOB) error, which is defined as the average proportion (out of 500 bootstrapped OOB datasets) of categories of sleep efficiency in the OOB data sets, incorrectly classified by the random forest model. Smaller OOB error values indicate higher accuracy of the random forest model.

Similar to the use of area under the curve (AUC) obtained from the Receiver Operating Characteristic (ROC) curve, random forest models also produce AUC and confusion matrix containing sensitivity, specificity, positive and negative predictive values. These metrics will also be used to assess the predictive values of random forest models in Aims #4 and 5.

Random forest models for Aims#4 and 5 will be fitted using the open source software R (version 3.5.0) and the randomForest package.

2.5.Limitations of the Proposed Study

First, the study population in Aims#1, 2 and 3 includes healthy community-dwelling older men, with few non-Caucasian participants. Thus, the results of this proposal might not be generalizable to women, others from different racial or ethnic groups, older men in poorer health, or those residing in other institutions like nursing homes. A second limitation of Aim#1 in this proposal is that since only men enrolled in Medicare FFS had available data on total healthcare and outpatient costs, hospital and SNF stays, results of Aim#1 might not be generalizable to men enrolled in Medicare Advantage. In addition, there is a great variability and noise in total healthcare and outpatient costs data, despite the use of rigorous statistical technique in Aim#1, it is possible that not all the variability and noise in healthcare costs data will be fully accounted for. Furthermore, while this proposal utilizes longitudinal cohort studies to look at the relationships between sleep disordered breathing and subsequent hospitalizations and costs in Aim#1, and between incident reduced sleep efficiency and a list of potential factors in Aims#2,3,4 and 5, causality of these relationships cannot be strongly inferred due to the potential for residual confounding. This proposal will only look incident reduced sleep efficiency in community-dwelling older men and women in Aims#2,3,4, and 5, thus future studies can examine incident reduced sleep efficiency in younger populations to compare results. Moreover, changes in other sleep parameters are also worth looking at in order to have a more comprehensive understanding of what affects sleep over time, which in turn helps target

certain patients' characteristics using intervention studies to improve sleep health of the general population and public health. All these limitations will be fully acknowledged in this study.

2.6. Timelines

These data sets have had IRB approvals and are included in the ongoing works for SOF and MrOS studies.

This dissertation follows a three manuscript format.

Aim #1 will be completed in Chapter 3 – Manuscript #1. At the time of the writing of this proposal, this manuscript has been in press at SLEEP journal. Aims #2 and 4 will be addressed in Chapter 4 – Manuscript #2. Aims #3 and 5 will form the third manuscript.

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Chapter 3: Manuscript 1

Association of Sleep-Disordered Breathing with Total Healthcare Costs and Utilization in Older Men: the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study

3.1.Overview

Study Objectives: To determine the associations of sleep-disordered breathing (SDB) with subsequent healthcare costs and utilization including inpatient and post-acute care facility stays among community-dwelling older men.

Methods: Participants were 1316 men (mean age 76.1 [SD=5.7] years) in the Outcomes of Sleep Disorders in Older Men (MrOS sleep) study (from December 2003 to March 2005), who were enrolled in a Medicare Fee-For-Service plan. Primary SDB measures including apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) were collected using in-home level 2 polysomnography. Incident healthcare costs and utilization were determined from claims data in the subsequent 3-year period post MrOS sleep visit.

Results: 529 (40.2%) men had ≥1 hospitalization in the 3-year period. Compared to those without sleep apnea (AHI <5/hour), men with moderate to severe sleep apnea (AHI ≥15/hour) had a higher odds of all-cause hospitalization (odds ratio [OR] adjusted for age and site 1.43, 95% confidence interval [CI] 1.07-1.90). This association was slightly attenuated after further adjustment for traditional prognostic factors including education, body mass index, comorbid medical conditions, and health status (OR=1.36; 95% CI 1.01-1.83). Similar associations were observed for ODI. However, measures of SDB were not

related to subsequent healthcare costs (total or outpatient) or odds of post-acute skilled nursing facility stay.

Conclusions: Older men with SDB have an increased risk of hospitalization, not entirely explained by the greater prevalence of comorbid conditions, but not higher subsequent total healthcare costs. These findings indicate a need to evaluate the impact of SDB treatment on subsequent healthcare utilization.

Keywords: sleep-disordered breathing, sleep apnea, Medicare, hospitalization, healthcare costs and utilizations, older men

3.2.Introduction

Sleep-disordered breathing (SDB) is a common disorder characterized by repeated pauses or reductions in breathing during sleep with a prevalence of 25% in older community dwelling men.[1,2] SDB is associated with prevalent and incident cardiovascular disease (CVD) including hypertension, coronary heart disease, cardiac conduction abnormalities, heart failure and stroke.[3-10] SDB is also associated with perioperative complications, motor vehicle accidents, cognitive impairment and cognitive decline.[11-13] Given that SDB is associated with adverse health outcomes, especially CVD events, SDB may be associated with higher healthcare costs and utilization across a variety of healthcare settings. If SDB is associated with higher subsequent healthcare costs and utilization, future intervention studies would be warranted to determine whether treatment of SDB lowers these measures of healthcare burden.

A number of studies primarily in younger or middle-aged populations have evaluated the association of SDB and healthcare utilization.[14-23] However, previous studies

were limited by use of cross-sectional or case-control study designs[16-19,22] and inadequate control of potential confounders including body mass index (BMI).[14,23] One study used the modified Chronic Disease Score (CDS) as a proxy measure for healthcare utilization[23] and another study relied on administrative claims for the diagnosis of the obstructive sleep apnea (OSA).[21] Only three studies focused on older men and results were not consistent between studies.[14,16,21]

Our aim was to examine the association of objective measures of SDB with subsequent total healthcare costs and utilization in community-dwelling older men. To address this question, we used a unique longitudinal data set comprised of 1316 men participating in the Outcomes of Sleep Disorders in Older Men (MrOS Sleep) prospective cohort study linked with their Medicare claims data.

3.3.Methods

3.3.1. Study population and Linkage to Medicare Claims Data

We studied participants enrolled in MrOS study, a prospective cohort study of 5994 community-dwelling older men, aged ≥65 years. Men were recruited between March 2000 to April 2002 from six US cities: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA. Details of the MrOS study design and recruitment have been described elsewhere.[24,25] Linkage of MrOS cohort data to Medicare Claims Files was completed by submitting participant social security and/or Medicare numbers to the Centers for Medicare and Medicaid Services (CMS). Linkage to Medicare enrollment data was successful for 5,876 men (98%) as of January 1, 1999.

Recruitment for Outcomes of Sleep disorders in Older Men (MrOS Sleep) study occurred from December 2003 to March 2005 among the pool of 5605 active participants (**Figure 3.1**). Among these men, 150 were not eligible for the MrOS Sleep Study because they were receiving treatment for sleep apnea or snoring, 1,997 were invited but refused to participate, and 323 were not asked to participate because recruitment goals had already been met. Thus, a total of 3135 (57%) men agreed to participate in the Sleep Study (exceeding the recruitment goal of 3000 men).

Of the 3135 men that participated in the sleep visit, 2911 men had usable overnight polysomnography (PSG) recording. Of these 2911 men, 1316 (45.2%) men who were enrolled continuously in a Medicare Fee-For-Service (FFS) program (Parts A and B [and not Part C, Medicare Advantage]) during the 12 months prior to and 36 months after the sleep visit (or until death within this period) were included in the analytical cohort for this study (**Figure 3.1**).

3.3.2. SDB exposures

In-home sleep studies were completed using in-home, level 2 polysomnography (Safiro, Compumedics, Inc.®, Melbourne, Australia). The PSG recordings were obtained within one month of the clinic visit (mean 6.9 ± 15.8 days from visit), with 78% of recordings gathered within one week of the clinic visit. The recording montage was as follows: C3/A2 and C4/A1 electroencephalograms, bilateral electrooculograms and a bipolar submental electromyogram to determine sleep stage; thoracic and abdominal respiratory inductance plethysmography to determine respiratory effort; airflow (by nasal-oral thermocouple and nasal pressure cannula); finger pulse oximetry (SpO2) for measuring oxygen saturation; lead I EKG; body position (mercury switch sensor); and

bilateral tibialis leg movements (piezoelectric sensors). Centrally-trained and certified staff performed home visits to set up the unit, verify the values of the impedances for each channel, confirm calibration of position sensors and note any problems encountered during set-up, similar to the protocol used in the Sleep Heart Health Study.[26] Staff returned the next morning to collect the equipment and download the data to the Central Sleep Reading Center (Cleveland, OH) to be scored by certified research polysomnologists blinded to all other data. PSG data quality was excellent, with a failure rate of less than 4% and more than 70% of studies graded as being of excellent or outstanding quality.

Apneas were defined as a complete or almost complete cessation of airflow for more than 10 seconds. Hypopneas were defined as a >30% reduction in amplitude of either respiratory effort or airflow for more than 10 seconds associated with an oxygen desaturation of ≥4%.[27]

The primary measures of SDB in this study were the apnea-hypopnea index (AHI) and oxygen desaturation index (ODI). AHI was defined as the average number of apneas and hypopneas per hour of sleep. Severity of sleep apnea was defined as normal if AHI was <5/hour, mild if AHI was 5 to <15/hour, and moderate to severe if AHI was ≥15/hour.[28] ODI was defined as the mean number of oxygen desaturation events (≥4% decrease in SpO2) per hour of sleep. Severity of ODI was considered normal if ODI ≤5/hour, mild if ODI was between 5 and ≤10/hour, moderate if ODI was between 10 and ≤15/hour, and severe if ODI >15/hour.[29] Secondary SDB measures included the percent of sleep time with SpO2 <90%, and OSA calculated as the sum of obstructive apneas (excluding central apneas) plus hypopneas associated with a ≥4% desaturation. Severity of nocturnal hypoxemia (% of total sleep time with SaO2 <90% [%TST<90]) was considered normal if

%TST<90 was less than 1%, mild if %TST<90 was 1.0% to less than 3.5%, and at least moderate if %TST<90 was 3.5% or greater. OSA severity was categorized using the same cutpoints as for AHI.

3.3.3. Outcome measures

The primary outcome was total healthcare costs (an aggregate measure of overall healthcare burden) for the 36 months after the MrOS sleep visit. Secondary outcomes included all-cause and CVD-related hospitalizations. Annualized total healthcare costs were calculated as the sum of standardized inpatient hospital costs, Part A paid skilled nursing facility (SNF) costs, inpatient rehabilitation facility (IRF) costs, outpatient costs, and home healthcare costs. Inpatient hospital stays and stays in post-acute care facilities (SNF or IRF) were identified using the Medical Provider Analysis and Review (MedPAR) file. Standardized costs for hospital stays, SNF stays and IRF stays were calculated using previously validated and published methods.[30-32] Costs for Part A paid SNF stays, for IRF stays, home healthcare utilization, and outpatient utilization were calculated using allowable charges for these services in the MedPAR, Home Healthcare, Carrier, and Outpatient Medicare claims files. All costs were adjusted for healthcare cost inflation to U.S. 2017 dollars.[32]

Secondary outcomes including all-cause hospitalizations, CVD-related hospitalizations and SNF stays were identified from claims data. A CVD-related hospitalization was defined as a hospitalization with a primary or secondary discharge diagnosis of coronary heart disease (ICD-9 codes 414.xx), congestive heart failure (ICD-9 codes 398.91, 428.0), myocardial infarction (ICD-9 codes 410.xx, 412, 429.7x) or cerebrovascular accident (stroke) (ICD-9 codes 433.xx, 434.xx).

3.3.4. Other measurements

Participants completed a questionnaire on demographics, history of selected medical conditions, self-reported health status, smoking status (never, former, current), at the time of the sleep visit. Participants were asked about physician diagnosis of diabetes, coronary heart disease (including angina, myocardial infarction, angioplasty, or coronary artery bypass), stroke, congestive heart failure, or chronic obstructive pulmonary disease (COPD). CVD was defined as having a self-reported history of coronary heart disease, stroke, or congestive heart failure. Hypertension was defined using self-reported hypertension, use of anti-hypertensive medications, having systolic blood pressure ≥140 mmHg, or having diastolic blood pressure ≥90 mmHg.[33] Depressive symptoms were assessed using the Geriatric Depression Scale (GDS); a participant with GDS score ≥6 was considered to have depression.[34] Participants who attended an in-clinic visit also had measurements of blood pressure, body weight and height collected. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Participants were also asked to bring all medication containers used within the preceding 30 days to the clinic visit. Drugs were identified and recorded by clinic staff, and the information was stored in an electronic drugs inventory database. All medications recorded by the clinics were entered into an electronic medications inventory (San Francisco Coordinating Center, San Francisco, CA). Each medication was matched to its Ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[35]

3.3.5. Statistical Analysis

Characteristics of the 1316 men were compared across categories of SDB measures using chi-square or Fisher's exact test for categorical variables, ANOVA for continuous variables with normal distributions and non-parametric Kruskal-Wallis tests for variables with skewed distributions.

The associations of SDB measures with annualized total healthcare costs and outpatient costs were estimated using generalized linear models (GLMs). GLMs with log link and gamma distribution were used to account for the highly right-skewed distributions of total healthcare costs and outpatient costs and to ensure that the models were well-specified based on the results of the Modified Park[36] and Pregibon link[37] tests. Logistic regression models were used to estimate the association of SDB measures with odds of one or more hospitalizations and odds of one or more SNF stays during the 3 year follow-up period.

Base models were adjusted for age and clinical site. Multivariable models were further adjusted for traditional prognostic variables including education, health status, diabetes, hypertension, CVD, COPD, and body mass index at the sleep visit.

Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina) or Stata, version 14 (StataCorp LLC, College Station, Texas).

3.4.Results

Study Population

Among the 1316 men in the analytic cohort, mean (standard deviation [SD]) age was 76.5 years (5.7); 92.2% were non-Hispanic white, and 12% reported their health status as fair/poor/very poor. There were 529 men (40.2%) who had no evidence of sleep apnea

as indicated by AHI <5/hour, 444 (33.7%) with mild sleep apnea (AHI 5 to <15/hour), and 343 (26.1%) with moderate to severe sleep apnea (AHI ≥15/hour). SDB as indicated by ODI was also common in this cohort of older men, with 21.0% of the study participants with ODI between 5 and ≤10/hour (mild), 12.8% with ODI between 10 and ≤15/hour (moderate), and 32.1% with ODI greater than 15/hour (severe). Men with greater severity of sleep apnea as manifested by higher AHI or ODI were older, more likely to report poorer health status and fewer years of education and have diabetes, hypertension, congestive heart failure and higher BMI. (**Table 3.1** and **Table S3.1**).

Characteristics (including the distributions of SDB measures) of the 1316 men in the analytical cohort were similar to those of the 1595 MrOS men attending the sleep visit who were excluded from analyses because they were not enrolled in a FFS plan (**Table S3.2**). While differences in race, educational level, hypertension, and depression were statistically significant, these differences were small in magnitude.

Associations of Measures of SDB with Total Healthcare and Outpatient Costs

The annualized unadjusted mean (SD) total healthcare and outpatient costs (2017 U.S. dollars) during the 36 month follow-up period were $7,499 (SD 9,552) and $3,908 (SD 4,813), respectively. Mean annualized total healthcare costs during the 3 years following the sleep visit were $7,441 (SD 9,904) for men without SDB, $6,945 (SD 8,644) for men with mild SDB, and $8,305 (SD 10,079) for men with moderate or more severe SDB (p-value for difference in mean total healthcare costs across categories of SDB=0.06, Table 1). After consideration of age and study enrollment site, there was no evidence of an association between severity of SDB as manifested by higher AHI or ODI and total healthcare costs (**Table 3.2**). For example, the cost ratios of mean total healthcare and

outpatient costs were slightly higher among men with moderate to severe sleep apnea (AHI ≥15/hour) compared with those without sleep apnea (AHI <5/hour), but the associations were not significant as shown by the respective cost ratios (CR) and the 95% confidence intervals (CI): 1.10 (0.92-1.31) and 1.01 (0.76-1.36). Further consideration of other potential confounders in multivariable models did not alter these results. Among secondary measures of SDB, neither OSA nor %TST<90 was associated with total healthcare costs. When considering outpatient costs, greater %TST<90 was associated with lower outpatient costs in full multivariable models.

Association of Measures of SDB with Incident All-Cause Hospitalization, CVD-Related Hospitalization and SNF Stay

There were 523 (39.7%) men who were hospitalized on at least 1 occasion during the three years following their polysomnography study including 272 (20.7%) with at least 1 CVD-related hospitalization (**Table 3.1**). A total of 77 men (5.9%) had at least 1 SNF stay and 88 (6.7%) men died during the 3 year-follow-up period.

Men with greater SDB as manifested by high levels of AHI, ODI, or OSA were more likely to experience at least 1 hospitalization including a CVD-related hospitalization during the subsequent 36 months. In particular, men with moderate to severe sleep apnea (AHI ≥15/hour) had a 1.4-fold higher odds of subsequent hospitalization (OR=1.43, 95% CI: 1.07-1.90) compared to those without sleep apnea (AHI <5/hour) in models adjusted for age and study enrollment site (**Table 3.3**). Results were similar in models substituting ODI or OSA for AHI. The association of moderate to severe SDB with hospitalization was only slightly attenuated in multivariate models further adjusted for additional potential confounders (OR for AHI ≥15/hour vs. <5/hour = 1.36, 95% CI: 1.01-1.83). The

associations of moderate to severe SDB as manifested by higher AHI, ODI, or OSA with odds of subsequent hospitalization due to CVD appeared to be similar in magnitude to associations of these measures with all-cause hospitalization, though the latter associations did not reach significance (**Table S3.3**). Associations of mild SDB as manifested by intermediate values of AHI, ODI or OSA the subsequent odds of hospitalization and CVD-related hospitalization were weaker in magnitude and not statistically significant. Among men hospitalized, there was no difference in mean length of hospital stays (LOS) according to severity of sleep apnea; mean LOS was 8.8 days for men without sleep apnea, 6.4 days for men with mild sleep apnea, and 8.1 days for those with moderate to severe sleep apnea. Greater nocturnal hypoxemia as manifested by higher %TST<90 was not related to odds of hospitalization. In addition, there was no association between any of the measures of SDB and odds of a SNF stay in either the minimally adjusted or fully adjusted models.

Additional Analyses

Further sensitivity analyses restricting the study sample to the 1228 men, who survived 36 months after the sleep visit did not alter the results (data not shown). In addition, analyses excluding the 72 (5.5%) men who initiated treatment for sleep apnea during the three-year follow-up period post sleep visit yielded similar results (data not shown).

3.5.Discussion

In this longitudinal study of older community-dwelling men, we found that SDB as manifested by higher AHI, ODI or OSA was similarly associated with a higher risk of hospitalization even after consideration of multiple traditional prognostic indicators.

However, measures of SDB were not related to healthcare costs or risk of post-acute skilled nursing facility stays. The presence of SDB may help identify individuals at increased risk for hospitalization. Future research should evaluate the effect of treatment of SDB on subsequent healthcare utilization.

Our findings suggest a 1.4-fold increase in the risk of hospitalization among older men with moderate to severe SDB, an association that is only explained in part by the greater burden of cardiovascular and other medical conditions among men with SDB. SDB is associated with chronic cardiac, pulmonary, metabolic and liver disease, which has been attributed to chronic effects of sleep fragmentation, increased work of breathing and hypoxemia. While we adjusted for prevalent health problems, those with moderate to severe SDB may have had more severe underlying organ dysfunction or less reserve, resulting in greater vulnerability to decompensation requiring in-patient hospitalization. SDB also has been associated with immune dysregulation and accelerated biological aging[38-40], which may accelerate inflammatory processes and reduce resiliency.[41] Individuals with underlying lung disease and SDB may have more hypoxemia than individuals with either condition and when faced with an exacerbation of lung disease, such individuals may more likely require hospitalization.[42] In addition, patients with SDB may be chronically fatigued and have impaired cognition, which may adversely impact adherence to chronic disease medical regiments.

Our results are in general agreement with other studies that have suggested that SDB is associated with increased risk of hospitalization.[17,18,21] A small case-control study (mean age 47.1 years), conducted in 1996 in Manitoba, Canada, comprised of 97 obese patients with OSA and 97 controls without OSA, reported that patients in the OSA group

had statistically significant higher total number of nights spent in hospitals during a two-year follow-up period (251 nights for OSA group vs. 90 nights for the control group).[17] Another Canadian case-control study reported similar findings where OSA patients spent more nights in hospitals than controls (1118 nights vs. 676 nights).[18] A large retrospective cohort study in 1,867,876 older veterans (age ≥65) done at the Veterans Health Administration (VHA) reported that patients with incident OSA had a 4.5-fold higher odds of hospitalization compared to those without OSA.[21] The magnitude of the association between OSA and hospitalization in these studies is higher than the magnitude of the association between SDB and hospitalization in our study. A plausible explanation for this difference in results may be the difference in the study design (case control vs. prospective cohort study). In addition, the retrospective cohort study performed at the VHA used the International Classification of Diseases (ICD-9) codes to obtain diagnosis of OSA that may not be as accurate as objectively measured OSA using polysomnography.[21] Our study strengthens and expands on these earlier findings through our use of objective, quantifiable measures of SDB through polysomnography, prospective design, and use of community-based sampling (rather than the common practice of clinic-based sampling) of older men not selected on the basis of disease status.

Few previous studies have estimated the associations between SDB and total healthcare costs and utilization in older men and arrived at inconsistent conclusions. Similar to findings from our study, a cross-sectional analysis of a small subgroup of 198 Taiwanese men at least 70 years of age, reported that there was no difference in the total healthcare costs between those with and without sleep apnea.[14] In contrast, utilizing a case-control study in an Israeli population, Tarasiuk et al. found that OSA patients had 1.8-fold

higher healthcare costs compared to controls without OSA in a small total sample of 185 older (age ≥65 years) patients.[16] Another cross-sectional study analyzed 6,440 participants (mean age 63.6 years) from the Sleep Heart Health Study (SHHS) and reported that severe SDB problems (AHI >29.9) and greater nocturnal hypoxemia were associated with higher healthcare utilization, as indirectly measured using the modified chronic disease score (CDS).[23] A small case-control study performed in middle-aged adults by Kapur et al. found that medical costs among patients with undiagnosed sleep apnea were almost double the medical costs for controls without sleep apnea, matched for age and gender, but this study did not consider other potential confounders of the association.[15] Potential reasons for these discrepant results could be due to other studies selection of either younger patients (SHHS) or sicker elderly patients compared to the healthier community-dwelling men in MrOS. For example, among the elderly group of 158 participants, Tarasiuk et al. reported 42% of them with poor health status; and among the OSA group, comorbidities such as CVD and hyperlipidemia were highly prevalent.[16] Compared to previously published studies, the advantages of our study include a prospective cohort design, consideration of several potential confounders and use of well-established Medicare claims data to estimate, with validated methods, standardized healthcare costs representative for the older male US Medicare population.

The increased risk of hospitalization for those with moderate to severe sleep apnea compared to those without sleep apnea did not translate to higher subsequent total healthcare costs, outpatient costs, or SNF utilization. Results were generally consistent regardless of which SDB measure was used. This casts doubt on the hypothesis that the costs of SDB treatment can be partially offset by saving health care costs associated with

untreated SDB. Results for sensitivity analyses restricting to those who survived at least 36 months following the sleep visit or excluding those who initiated treatment for SDB during follow-up were similar to finding of the primary analyses. Surprisingly, we found that men with moderate to severe nocturnal hypoxemia had lower outpatient costs compared to men without hypoxemia in the full multivariable model. We do not have a plausible explanation for this finding that may be a spurious result due to random chance alone or numerous comparisons performed. Hence, while treatment of sleep apnea may yield health benefits, our data suggest that lower healthcare costs will likely not be among those benefits.

This study has several strengths, including the use of a prospective cohort study with comprehensively assessed participant characteristics, objective measures of SDB using polysomnography, enrollment of participants not on the basis of sleep apnea status, published and validated methodology to compute standardized healthcare costs and ascertain healthcare utilization from administrative data, linkage of cohort participants to their Medicare claims data; and inclusion of several possible confounding and mediating factors. However, this study has limitations. First, the cohort included healthy community-dwelling older men, with few non-Caucasian participants. Thus, the results might not be generalizable to women, others from different racial or ethnic groups, older men in poorer health, or those residing in other institutions like nursing homes. Future studies are needed to confirm our findings and to further investigate associations of SDB and other outcomes, such as long-term nursing home placement. Second, data on total healthcare and outpatient costs, hospital and SNF stays were only available for those men enrolled in Medicare FFS, but not for those enrolled in Medicare Advantage. This limitation is mitigated by the fact that characteristics of men enrolled in Medicare FFS, including proportions with SDB,

were similar to those of men enrolled in Medicare Advantage. Third, while our data does not preclude a weak association between moderate to severe sleep apnea and higher total health care cost, the association was not significant perhaps because we did not have a sufficient sample size in the moderate to severe sleep apnea group to detect a small effect. Fourth, we do not have the sample size to establish if shifts of costs from outpatient or SNF settings to acute care hospitals account for our findings of higher odds of hospitalization yet no clear increase in total health care costs amongst those with obstructive sleep apnea. Fifth, while we adjusted for education in our analysis, we did not account for other socioeconomic status variables such as income and occupation, which might have confounded the association between sleep apnea and healthcare costs and utilization. Finally, even though we utilized a longitudinal cohort study and controlled for potential confounders and mediators, causality of the relationship between SDB and risk of subsequent hospitalizations cannot be strongly inferred due to the potential for residual confounding.

In conclusion, our results suggest that SDB is associated with higher risk of hospitalization (but not with total healthcare costs) in community-dwelling older men. This association is not entirely explained by a greater number of cardiovascular or medical conditions among those men with SDB. Future studies are needed to evaluate the association between SDB and healthcare costs and utilization among other patient populations and to evaluate the effect of treatment of SDB on these measures of healthcare burden.

3.6.Figures, tables and supplemental tables

Figure 3.1. Analysis Cohort

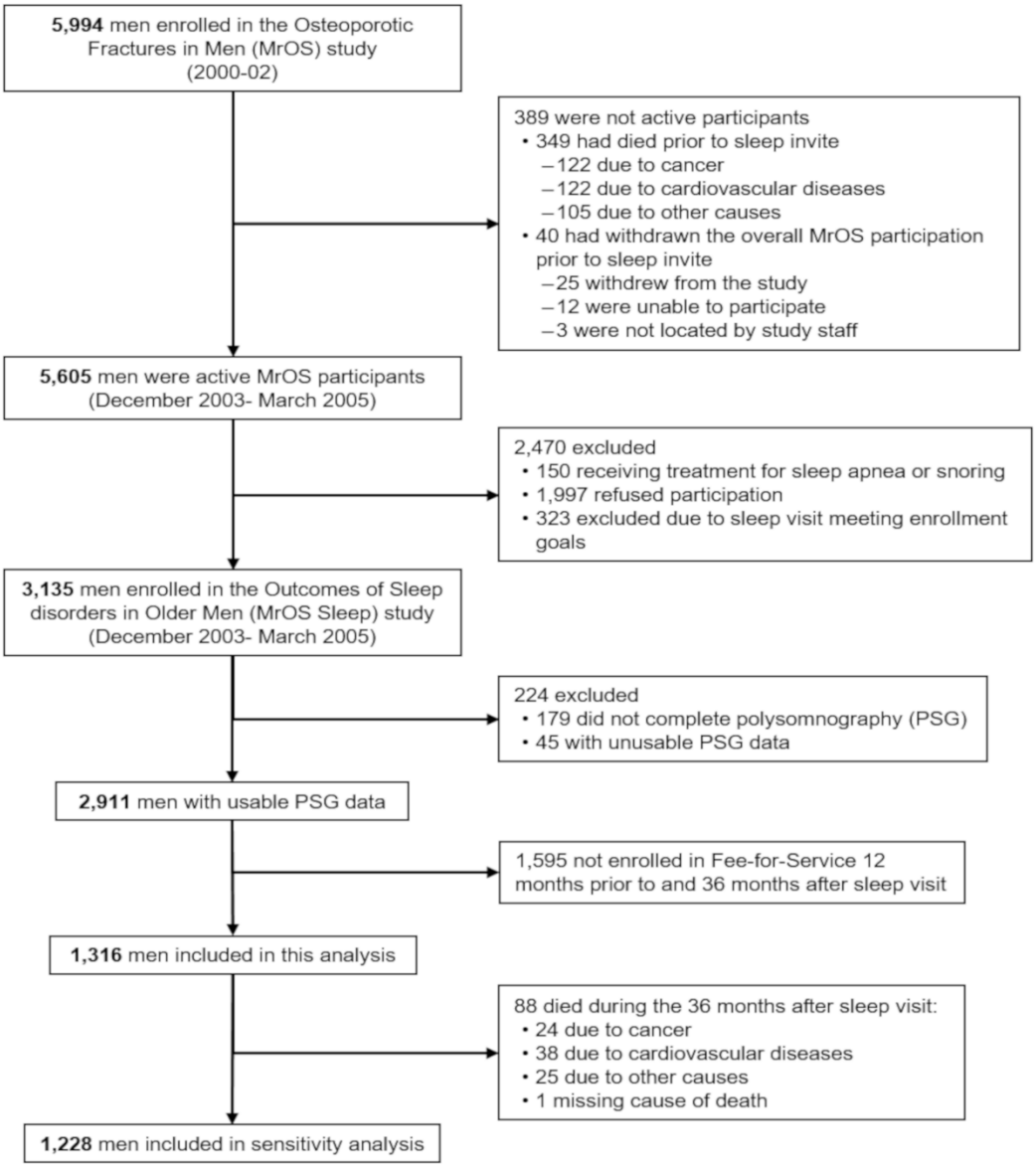

Table 3.1. Characteristics of 1316 Participants by Category of Apnea Hypopnea Index at Baseline

Baseline Characteristic	AHI			P-value*
	Normal (<5.0/hour) (N=529)	Mild (5.0 to <15/hour) (N=444)	At Least Moderate (≥15/hour) (N=343)	
Age, years, mean (SD)	76.2 (5.7)	76.2 (5.7)	77.3 (5.6)	0.01
Caucasian, n (%)	489 (92.4)	411 (92.6)	313 (91.3)	0.76
Education, n (%)				0.02
Less than high school	17 (3.2)	20 (4.5)	14 (4.1)	
High school	56 (10.6)	58 (13.1)	63 (18.4)	
Beyond high school	456 (86.2)	366 (82.4)	266 (77.6)	
Fair, Poor or very poor health status, n (%)	53 (10.0)	60 (13.5)	45 (13.1)	0.19
Smoking status, n (%)				0.23
Never	216 (40.8)	181 (40.9)	147 (42.9)	
Past	302 (57.1)	254 (57.3)	195 (56.9)	
Current	11 (2.1)	8 (1.8)	1 (0.3)	
Diabetes, n (%)	54(10.2)	61 (13.8)	53 (15.5)	0.06
Hypertension, n (%)	344 (65.0)	316 (71.3)	262 (76.6)	0.001
Coronary heart disease†, n (%)	161 (30.4)	124 (27.9)	114 (33.2)	0.27
Stroke, n (%)	23 (4.3)	15 (3.4)	11 (3.2)	0.62
Congestive heart failure, n (%)	18 (3.4)	30 (6.8)	25 (7.3)	0.02
CVD**, n (%)	178 (33.6)	144 (32.4)	130 (37.9)	0.25
COPD or emphysema, n (%)	29 (5.5)	24 (5.4)	11 (3.2)	0.25

Body mass index, kg/m^2, mean (SD)	26.2 (3.3)	27.3 (3.6)	28.2 (4.1)	<0.001
Depression (GDS score ≥6), n (%)	31 (5.9)	17 (3.8)	23 (6.7)	0.17
Hospitalized in the year prior to sleep visit, n (%)	67 (12.7)	65 (14.6)	43 (12.5)	0.59
Outcomes‡				
Hospitalized, n (%)	188 (35.5)	176 (39.6)	159 (46.4)	0.006
CVD-related hospitalization, n (%)	96 (18.1)	87 (19.6)	89 (25.9)	0.02
SNF stay, n (%)	34 (6.4)	24 (5.4)	19 (5.5)	0.76
Dead, n (%)	32 (6.0)	29 (6.5)	27 (7.9)	0.55
Annualized total healthcare costs				0.06
Mean (SD)	$7,441 (9,904)	$6,945 (8,644)	$8,305 (10,079)	
Median (IQR)	$3,672 (1,536 to 9,128)	$3,746 (1,641 to 8,799)	$4,674 (1,947 to 10,227)	
Annualized outpatient costs				0.16
Mean (SD)	$3,955 (5,192)	$3,641 (3,962)	$4,181 (5,193)	
Median (IQR)	$2,772 (1,344 to 4,950)	$2,708 (1,287 to 4,632)	$2,980 (1,601 to 5,064)	

Abbreviations: AHI = Apnea Hypopnea Index; N = number of men in each category; SD = standard deviation; n (%) = number (proportion); CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; GDS = Geriatric Depression Scale; SNF = skilled nursing facility; IQR = interquartile range

*ANOVA (or non-parametric equivalent i.e. Kruskal Wallis test) for continuous variables, chi-square (or Fisher's exact test) for categorical variables

†Coronary heart disease was defined by a self-reported history of a physician diagnosis of angina, myocardial infarction, angioplasty or coronary artery bypass

**CVD was defined as having either one these three conditions: CHD, stroke, or congestive heart failure

‡During the 3 year follow up post MrOS sleep visit

Table 3.2. Associations of Measures of Sleep Disordered Breathing with Mean Total and Outpatient Healthcare Costs

	Cost Ratio (95% CI)			
	Total Healthcare Costs		Outpatient Care Costs	
SDB measure	Age and Site adjusted	Multivariable adjusted*	Age and Site adjusted	Multivariable adjusted*
AHI†				
<5.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
5.0 to <15.0	0.93 (0.79-1.10)	0.91 (0.78-1.08)	0.87 (0.66-1.14)	0.86 (0.66-1.13)
≥15.0	1.10 (0.92-1.31)	1.04 (0.86-1.24)	1.01 (0.76-1.36)	0.93 (0.69-1.25)
ODI†				
<5.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
5.0 to ≤10	0.95 (0.78-1.15)	0.95 (0.78-1.16)	0.94 (0.68-1.29)	0.93 (0.68-1.27)
10 to ≤15	0.87 (0.69-1.10)	0.86 (0.68-1.09)	0.74 (0.51-1.07)	0.72 (0.50-1.04)
>15.0	1.07 (0.90-1.28)	1.01 (0.84-1.21)	0.93 (0.70-1.23)	0.84 (0.63-1.13)
OSA†				
<5.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
5.0 to <15.0	0.96 (0.81-1.14)	0.94 (0.80-1.11)	0.87 (0.67-1.15)	0.86 (0.66-1.13)
≥15.0	1.10 (0.92-1.31)	1.06 (0.89-1.27)	1.01 (0.76-1.35)	0.95 (0.71-1.27)
%TST<90				
<1.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1.0 to <3.5	1.02 (0.86-1.22)	0.97 (0.81-1.15)	0.88 (0.66-1.17)	0.80 (0.61-1.06)
≥3.5	0.98 (0.82-1.17)	0.95 (0.78-1.14)	0.78 (0.59-1.04)	0.68 (0.51-0.90)

Abbreviations: CI = confidence interval; SDB = sleep disordered breathing; AHI = apnea hypopnea index; ODI = oxygen desaturation index; OSA = obstructive apneas plus hypopneas with a 4% desaturation; %TST<90 = percent of total sleep time with oxygen saturation <90%

*Adjusted for age, site, education, health status, comorbid medical conditions (including diabetes, hypertension, CVD, and COPD), and body mass index at the sleep visit

†Unit is per hour

Table 3.3. Associations of Measures of Sleep Disordered Breathing with Odds of Hospitalization and Skilled Nursing Facility Stays

	Odds Ratio (95% CI)			
	Inpatient Hospital Stays		SNF Stays	
SDB measure	Age and Site adjusted	Multivariable adjusted*	Age and Site adjusted	Multivariable adjusted*
AHI†				
<5.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
5.0 to <15.0	1.15 (0.88-1.50)	1.13 (0.86-1.49)	0.85 (0.49-1.48)	0.72 (0.41-1.28)
≥15.0	1.43 (1.07-1.90)	1.36 (1.01-1.83)	0.80 (0.44-1.46)	0.60 (0.32-1.13)
ODI†				
<5.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
5.0 to ≤10	0.96 (0.70-1.33)	0.96 (0.69-1.33)	0.45 (0.20-1.00)	0.44 (0.19-0.98)
10 to ≤15	1.32 (0.92-1.92)	1.33 (0.91-1.93)	0.78 (0.36-1.72)	0.67 (0.30-1.49)
>15.0	1.38 (1.04-1.83)	1.33 (0.99-1.78)	1.02 (0.59-1.76)	0.75 (0.42-1.34)
OSA†				
<5.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
5.0 to <15.0	1.09 (0.83-1.44)	1.07 (0.81-1.41)	0.79 (0.45-1.39)	0.67 (0.37-1.20)
≥15.0	1.41 (1.06-1.88)	1.37 (1.02-1.84)	0.80 (0.45-1.42)	0.61 (0.33-1.13)
%TST<90				
<1.0	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1.0 to <3.5	1.04 (0.79-1.38)	1.00 (0.75-1.34)	0.97 (0.54-1.74)	0.82 (0.45-1.51)
≥3.5	1.22 (0.93-1.62)	1.20 (0.89-1.61)	1.11 (0.62-1.97)	0.82 (0.44-1.53)

Abbreviations: CI = confidence interval; SNF = skilled nursing facility; SDB = sleep disordered breathing; AHI = apnea hypopnea index; ODI = oxygen desaturation index; OSA = obstructive apneas plus hypopneas with a 4% desaturation; %TST<90 = percent of total sleep time with oxygen saturation <90%

*Adjusted for age, site, education, health status, comorbid medical conditions (including diabetes, hypertension, CVD, and COPD), and body mass index at the sleep visit

†Unit is per hour

Table S3.1. Characteristics of 1316 Participants by Category of Oxygen Desaturation Index at Baseline

	Oxygen Desaturation Index				
Baseline Characteristic	**Normal (≤5/hour) (N=449)**	**Mild (5 to ≤10/hour) (N=276)**	**Moderate (10 to ≤15/hour) (N=168)**	**Severe (>15/hour) (N=423)**	**P-value***
Age, years, mean (SD)	76.1 (5.8)	75.8 (5.5)	76.5 (5.6)	77.3 (5.6)	0.005
Caucasian, n (%)	410 (91.3)	262 (94.9)	157 (93.5)	384 (90.8)	0.18
Education, n (%)					0.008
Less than high school	15 (3.3)	10 (3.6)	10 (6.0)	16 (3.8)	
High school	43 (9.6)	32 (11.6)	26 (15.5)	76 (18.0)	
Beyond high school	391 (87.1)	234 (84.8)	132 (78.6)	331 (78.3)	
Fair, poor or very poor health status, n (%)	49 (10.9)	21 (7.6)	24 (14.3)	64 (15.2)	0.02
Smoking status, n (%)					0.37
Never	184 (13.9)	104 (7.9)	69 (5.3)	187 (14.2)	
Past	254 (19.3)	169 (12.9)	97 (7.4)	231 (17.6)	
Current	11 (0.8)	3 (0.2)	2 (0.2)	4 (0.3)	
Diabetes, n (%)	45 (10.0)	29 (10.5)	26 (15.5)	68 (16.1)	0.02
Hypertension, n (%)	296 (65.9)	182 (65.9)	122 (72.6)	322 (76.5)	0.002
Coronary heart disease†, n (%)	136 (30.3)	75 (27.2)	49 (29.2)	139 (32.9)	0.44
Stroke, n (%)	19 (4.2)	12 (4.3)	5 (3.0)	13 (3.1)	0.71
Congestive heart failure, n (%)	16 (3.6)	16 (5.8)	7 (4.2)	34 (8.1)	0.03
CVD**, n (%)	151 (33.6)	92 (33.3)	52 (31.0)	157 (37.1)	0.47
COPD or emphysema, n (%)	26 (5.8)	13 (4.7)	12 (7.1)	13 (3.1)	0.13
Body mass index, kg/m^2, mean (SD)	26.0 (3.1)	26.9 (3.5)	27.8 (3.6)	28.2 (4.1)	<0.001
Depression (GDS score ≥6), n (%)	26 (5.8)	12 (4.4)	4 (2.4)	29 (6.9)	0.14

Hospitalized in the year prior to sleep visit, n (%)	56 (12.5)	36 (13.0)	23 (13.7)	60 (14.2)	0.90
Outcomes‡					
Hospitalized, n (%)	159 (35.4)	96 (34.8)	74 (44.0)	194 (45.9)	0.003
CVD-related hospitalization, n (%)	78 (17.4)	51 (18.5)	37 (22.0)	106 (25.1)	0.03
SNF stay, n (%)	30 (6.7)	8 (2.9)	9 (5.4)	30 (7.1)	0.08
Dead, n (%)	25 (5.6)	18 (6.5)	10 (6.0)	35 (8.3)	0.45
Annualized total healthcare costs					
Mean (SD)	$7,387 (9,839)	$7,064 (9,606)	$6,736 (7,469)	$8,204 (9,924)	0.27
Median (IQR)	$3,561 (1,551 to 9,079)	$3,566 (1,643 to 8,923)	$3,966 (1,697 to 8,285)	$4,621 (1,806 to 10,475)	
Annualized outpatient costs					
Mean (SD)	$4,077 (5,483)	$3,839 (4,340)	$3,419 (3,412)	$3,968 (4,823)	0.59
Median (IQR)	$2,806 (1,404 to 4,978)	$2,711 (1,279 to 4,822)	$2,634 (1,427 to 4,219)	$2,867 (1,472 to 4,931)	

Abbreviations: N = number of men in each category; SD = standard deviation; n (%) = number (proportion); CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; GDS = Geriatric Depression Scale; SNF = skilled nursing facility; IQR = interquartile range

*ANOVA (or non-parametric equivalent i.e. Kruskal Wallis test) for continuous variables, chi-square (or Fisher's exact test) for categorical variables

†Coronary heart disease was defined by a self-reported history of a physician diagnosis of angina, myocardial infarction, angioplasty or coronary artery bypass

**CVD was defined as having either one these three conditions: coronary heart disease, stroke or congestive heart failure

‡During the 3 year follow up post MrOS sleep visit

Table S3.2. Characteristics of 2911 Participants According to Enrollment Status

Characteristic	All Participants (N=2911)	FFS Enrollment		P-value*
		Yes (N=1316)	No (N=1595)	
Age, years, mean (SD)	76.4 (5.5)	76.5 (5.7)	76.3 (5.4)	0.39
Caucasian, n (%)	2641 (90.7)	1213 (92.2)	1428 (89.5)	0.01
Education, n (%)				<0.001
Less than high school	152 (5.2)	51 (3.9)	101 (6.3)	
High school	472 (16.2)	177 (13.4)	295 (18.5)	
Beyond high school	2287 (78.6)	1088 (82.7)	1199 (75.2)	
Fair, poor or very poor health status, n (%)	2524 (86.8)	1157 (88.0)	1367 (85.8)	0.08
Smoking, n (%)				0.07
Never	1150 (39.5)	544 (41.4)	606 (38.0)	
Past	1703 (58.5)	751 (57.1)	952 (59.7)	
Current	57 (2.0)	20 (1.5)	37 (2.3)	
Diabetes, n (%)	387 (13.3)	168 (12.8)	219 (13.7)	0.45
Hypertension, n (%)	1986 (68.3)	922 (70.2)	1064 (66.7)	0.05
Coronary heart disease†, n (%)	869 (29.9)	399 (30.3)	470 (29.5)	0.62
Stroke, n (%)	111 (3.8)	49 (3.7)	62 (3.9)	0.82
Congestive heart failure, n (%)	174 (6.0)	73 (5.6)	101 (6.3)	0.38
CVD**, n(%)	989 (34.0)	537 (33.7)	452 (34.3)	0.70
COPD or emphysema, n (%)	151 (5.2)	64 (4.9)	87 (5.5)	0.48
Body mass index, kg/m^2, mean (SD)	27.2 (3.8)	27.1 (3.7)	27.2 (3.9)	0.37
Depression (GDS score ≥6), n(%)	188 (6.5)	117 (7.3)	71 (5.4)	0.04
AHI				0.66
<5.0/hour	1144 (39.3)	529 (40.2)	615 (38.6)	
5.0 to <15.0/hour	999 (34.3)	444 (33.7)	555 (34.8)	
≥15.0/hour	768 (26.4)	343 (26.1)	425 (26.6)	

ODI				0.62
<5.0/hour	971 (33.4)	449 (34.1)	522 (32.7)	
5.0 to ≤10/hour	617 (21.2)	276 (21.0)	341 (21.4)	
10 to ≤15/hour	396 (13.6)	168 (12.8)	228 (14.3)	
>15.0/hour	927 (31.8)	423 (32.1)	504 (31.6)	
OSA				0.57
<5.0/hour	1050 (36.1)	487 (37.0)	563 (35.3)	
5.0 to <15.0/hour	1012 (34.8)	446 (33.9)	566 (35.5)	
≥15.0/hour	849 (29.2)	383 (29.1)	466 (29.2)	
%TST<90				0.14
<1.0	1410 (48.4)	639 (48.6)	771 (48.3)	
1.0 to <3.5	767 (26.3)	327 (24.8)	440 (27.6)	
≥3.5	734 (25.2)	350 (26.6)	384 (24.1)	

Abbreviations: FFS = Fee-for-Service; N = number of men in each category; SD = standard deviation; n (%) = number (proportion); CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; GDS = Geriatric Depression Scale; AHI = apnea hypopnea index; ODI = oxygen desaturation index; OSA = obstructive apneas plus hypopneas with a 4% desaturation; %TST<90 = percent of total sleep time with oxygen saturation <90%

*T-test (or non-parametric equivalent i.e. Wilcoxon rank-sum test) for continuous variables, chi-square (or Fisher's exact test) for categorical variables

†Coronary heart disease was defined by a self-reported history of a physician diagnosis of angina, myocardial infarction, angioplasty or coronary artery bypass

**CVD was defined as having either one these three conditions: coronary heart disease, stroke or congestive heart failure

Table S3.3. Associations of Measures of Sleep Disordered Breathing with Subsequent CVD-related Hospitalization

	Inpatient Hospital Stays, Odds Ratio (95% CI)	
SDB measure	Age and Site Adjusted	Multivariable Adjusted*
AHI		
<5.0/hour	1.00 (referent)	1.00 (referent)
5.0 to <15.0/hour	1.04 (0.74-1.44)	1.06 (0.74-1.51)
≥15.0/hour	1.38 (0.98-1.95)	1.32 (0.91-1.91)
ODI		
<5.0/hour	1.00 (referent)	1.00 (referent)
5.0 to ≤10/hour	1.05 (0.71-1.57)	1.04 (0.68-1.59)
10 to ≤15/hour	1.20 (0.76-1.88)	1.28 (0.78-2.08)
>15.0	1.36 (0.97-1.92)	1.34 (0.92-1.95)
OSA		
<5.0/hour	1.00 (referent)	1.00 (referent)
5.0 to <15.0/hour	1.06 (0.76-1.48)	1.04 (0.73-1.49)
≥15.0/hour	1.22 (0.87-1.72)	1.21 (0.84-1.76)
%TST<90		
<1.0	1.00 (referent)	1.00 (referent)
1.0 to <3.5	1.19 (0.85-1.66)	1.10 (0.77-1.59)
≥3.5	1.04 (0.74-1.46)	1.14 (0.78-1.67)

Abbreviations: CI = confidence interval; SDB = sleep disordered breathing; AHI = apnea hypopnea index; ODI = oxygen desaturation index; OSA = obstructive apneas plus hypopneas with a 4% desaturation; %TST<90 = percent of total sleep time with oxygen saturation <90%

*Adjusted for age, site, education, health status, comorbid medical conditions (including diabetes, hypertension, CVD, and COPD), and body mass index at the sleep visit

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Chapter 4: Manuscript 2

Predictors of incident reduced sleep efficiency in community-dwelling older women

4.1.Overview

Study objectives: To examine potential risk factors for incident reduced sleep efficiency among community-dwelling women in the 9th decade of life

Methods: Participants were 700 women (mean age 82.5 [SD=3.0] years) with normal sleep efficiency (SE >=70%) at SOF Visit 8 exam (2002-2004) of the Study of Osteoporotic Fractures (SOF), who had repeated measurement of sleep efficiency at the SOF Visit 9 exam (2006-2008). Sleep efficiency at both time points was measured using actigraphy collected for a minimum of 3 consecutive 24-hour periods (mean duration, 3.6 days). Incident reduced SE was defined by a SE <70% at Visit 9. Logistic regression was used to estimate the associations of potential predictors with incident reduced sleep efficiency in minimally and fully adjusted models. Variable importance measures obtained from random forest analysis were used to rank predictors most important in predicting incident reduced sleep efficiency.

Results: 62 (8.9%) women developed incident reduced sleep efficiency between SOF Visits 8 and 9. The odds of developing incident reduced sleep efficiency obtained from the multivariable logistic regression models were higher among women with history of antidepressant use (adjusted odds ratio (OR) = 3.06, 95% confidence interval (CI): 1.50, 6.25), benzodiazepine use (OR=2.97, 95% CI: 1.30, 6.80), and self-reported hypertension (OR = 2.83, 95% CI: 1.47, 5.45). Random forest identified the use of benzodiazepine as

the most important factor in predicting incident reduced sleep efficiency, followed by depressive symptoms, self-reported health status, anxiety, and frailty. Both random forest and logistic regression identified benzodiazepine as a common determinant of incident reduced sleep efficiency.

Conclusions: These results from logistic regression and random forest suggest that the antidepressant use, benzodiazepine use, hypertension, depression, health status, anxiety and frailty may be factors of importance in the development of reduced sleep efficiency in women late in life. Future studies are warranted to explore potential biological mechanisms underlying these associations. In addition, machine learning technique via random forests and other supervised and unsupervised techniques should be used in sleep research to compare findings.

Keywords: incident reduced sleep efficiency, actigraphy, older women, logistic regression, machine learning, random forests.

4.2.Introduction

Sleep efficiency, defined as the percentage of time in bed spent sleeping, is a key measure of sleep health and has been shown to decrease with advancing age.[1–3] Sleep efficiency below 70% is associated with increased mortality risk in older adults, and has been proposed as the primary parameter to be assessed and targeted to promote optimal sleep health in older adults.[4] Furthermore, reduced sleep efficiency is associated with impaired cognitive function and higher rates of cognitive decline in older women[5].

While some studies have examined sleep efficiency as a predictor of adverse health outcomes and conditions, there is a paucity of research that has considered sleep efficiency as an outcome measure. A Canadian study examined factors associated with sleep efficiency among 2,468 community-dwelling men and women 65 years of age and older (mean age = 73.7 [SD = 6.1].[6] The study found that pain, nocturia, sleep medication use and awakening from bad dreams were predictive of having a sleep efficiency below 80%. However, this study had several limitations including a cross-sectional design and use of interviews to assess self-reported efficiency rather than an objective measure such as actigraphy or polysomnography.

Given that reduced sleep efficiency is associated with increased risk of adverse outcomes in older adults, longitudinal research is warranted to identify predictors of the development of incident reduced sleep efficiency. Identifying the determinants of objectively measured sleep efficiency in the elderly population is particularly important for informing evidence-based recommendations on which factors to target or interventions to implement to improve sleep health among this population. For example, the development

of incident reduced sleep efficiency may be a cause, marker or consequence of developing adverse health conditions and diseases.

The present study aimed to longitudinally examine and identify factors associated with incident reduced sleep efficiency in 700 U.S. older community-dwelling women enrolled in the Study of Osteoporotic Fractures (SOF), using the traditional logistic regression. In addition, we applied the random forest technique to identify factors most important in predicting incident reduced sleep efficiency in U.S. older community-dwelling women. Random forest, a machine learning technique has been developed to solve classification problems in the last 15 years.[7] Random forest technique works well with both small sample sizes and complex data structures including high dimensional data. It is also robust to noise and takes each individual predictor including non-linear data and multivariate interactions between predictors into account. As a result, random forest algorithm has been applied to many fields such computational biology, personalized medicine and engineering, etc. and has been proven to perform better and produce higher accuracy than other classification algorithms.[8–13] Finally, the results obtained from logistic regression were contrasted with those obtained from the random forest technique.

4.3.Methods

4.3.1. Study population

We studied participants enrolled in the SOF study, a longitudinal cohort study of community-dwelling older women, aged ≥65 years. Women were recruited from four U.S. cities: Baltimore, MD; Minneapolis, MN; Portland, OR; and Monongahela Valley near Pittsburgh, PA.[14] At the baseline SOF visit women were excluded if they were unable to

walk without help or had previous bilateral hip replacements. From September 1986 to October 1988, 9,704 white women were recruited. African American women were initially excluded due to their low incidence of hip fracture. However, from February 1997 to February 1998 (Visit 6), 662 African American women met study inclusion criteria and were recruited into the study.[15] We included women who completed both wrist actigraphy during the SOF Visit 8 (2002-2004) and during the SOF Visit 9 (2006-2008). At the SOF Visit 9, only women from three of the original four sites were enrolled into the study (Minneapolis, MN; Portland, OR; and Monongahela Valley near Pittsburgh, PA).

Of the 4,727 women who completed at least the SOF Visit 8 questionnaire, actigraphy data were collected on 3,127 (62.2%) women who completed clinic or home visit. Of these, 1793(57.3%) were enrolled at the 3 sites conducting visit 9. A total of 829 women (46.2% of women completing at least the questionnaire component at visit 9) had repeated actigraphy data at the SOF Visit 9 (5.0 years [SD=0.5] between visits. We excluded 128 women who had sleep efficiency <70% at the SOF Visit 8 and one woman with missing repeat sleep efficiency at the SOF Visit 9. The remaining 700 women are included in the present analysis (**Figure 4.1**).

The institutional review boards on human research approved the study at each institution. All participating women provided informed consent.

4.3.2. Actigraphy

Actigraphy is an objective non-invasive method of collecting information on activity and rest cycles. In this study, actigraphy was performed using the Octagonal Sleep Watch actigraphy, or SleepWatch-O, (Ambulatory Monitoring, Inc, Ardsley, NY) to

estimate sleep/wake activity. The actigraph, which looks like a wristwatch, measures movement using a piezoelectric biomorph-ceramic cantilevered beam, which generates a voltage each time the actigraph is moved. These voltages are gathered continuously and stored in one-minute epochs. The term "mode" is used to refer to the technique with which different measures were obtained. Data were collected in the 3 modes of zero crossings (ZCM), proportional integration mode (PIM), and time above threshold (TAT). In ZCM mode the conditioned transducer signal is compared with a sensitivity threshold of zero. The number of times the signal voltage crosses zero voltage is summed over the epoch. The ZCM mode is a measure of frequency of movement. The PIM mode is a high-resolution measurement of the area under the rectified conditioned transducer signal (area under the curve). The PIM mode is a measure of activity level or vigor of motion. In TAT mode the amount of time in tenths of a second spent above the sensitivity threshold is gathered over the epoch. The TAT mode measures time spent in motion or duty-cycle.[16]

Actigraphy data were transferred to the San Francisco Coordinating Center (San Francisco, CA) for centralized processing. Centralized training and certification was required for clinic staff gathering actigraphy data. Action W-2 software was used to score the data.[17] Sleep scoring algorithms available in this software were used to determine sleep from wake times. The Cole-Kripke algorithm was used for data collected in the ZCM mode and the University of California, San Diego (UCSD) scoring algorithm was used for data collected in the PIM and TAT modes.[18,19] These algorithms calculate a moving average, which takes into account the activity levels immediately prior to and after the current minute to determine if each timepoint should be coded as sleep or wake. Participants

completed a sleep diary which was used in the editing of the data to determine when the participant got into and out of bed and when the actigraph was removed.[20] In this present study, data collected from PIM mode were used because PIM mode matches up better (than TAT and ZCM) to PSG which is the gold standard for measuring sleep parameters by electroencephalograms (EEG).[21]

In SOF, women wore the actigraphs on the nondominant wrist for a minimum of 3 consecutive 24-hour periods, except when bathing or during water sports.

4.3.3. Outcome variable

Sleep efficiency was defined as the percentage of time spent sleeping during the entire in-bed interval. Incident reduced sleep efficiency was calculated from actigraphy results at two time points. A woman was classified as having incident reduced sleep efficiency if she had normal sleep efficiency (SE >= 70%)) at SOF Visit 8 and reduced sleep efficiency (SE < 70%) at SOF Visit 9.

4.3.4. Predictors of incident reduced sleep efficiency

4.3.4.1. Demographic and lifestyle factors

At the SOF Visit 8, women completed questionnaires on demographics (age (continuous), race (white vs. black), highest education obtained (years), Women were classified as married or not married (a category that included widowed, divorced, separated, or never married). In addition, participants reported lifestyle factors including smoking history (yes/no), and alcohol use (number of drinks/week), physical activity (none vs. at least walked for exercise or engaged in vigorous activities).

4.3.4.2. General and physical health

Women were asked to report health status (excellent/good vs. fair/poor/very poor) and a physician diagnosis (yes/no) of selected medical conditions including hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus. Usual gait speed was measured using the 6-meter walk speed in meter/second. The presence of impairment in Instrumental Activities of Daily Living (IADL) was determined by asking the participants if they had difficulty of doing the following five instrumental activities of daily living: heavy housework, walking 2 to 3 blocks, climbing 10 stairs, shopping for groceries or clothing, and preparing meals on her own.[22,23] A woman was considered to have an IADL impairment (yes vs.no) if they reported difficulty on at least one activity. Frailty was defined using the SOF index[24] created for use in the clinical practice setting and was identified if data was available for at least two of the following three components of SOF frailty index: 1) weight loss of ≥5% between SOF visit 6 and SOF visit 8, regardless of whether a woman was trying to lose weight or not; 2) unable to stand up from a chair five times without using the arms; and 3) reporting poor energy by having an answer of "No" to the question "Do you feel full of energy?" on the Geriatric Depression Scale. A woman was considered robust if she had none of these three components, intermediate (pre-frail) if she had 1 component and frail if she had at least 2 components.

4.3.4.3. Mental health

Depressive symptoms were assessed using the Geriatric Depression Scale (GDS-15)[25]; a participant with GDS-15 score ≥6 was considered to have depression. A woman was considered to have significant anxiety symptoms (yes/no) if her Goldberg anxiety score was ≥5[26]. Cognitive function was measured using the Mini-Mental State Examination, scored from 0 to 30[27] and the Trails B test.[28]

4.3.4.4. Prescription drug use

Women were asked to bring all current (defined as daily or almost daily use in the 30 days preceding the examination) prescription and nonprescription medications with them to SOF clinic Visit 8. Subsequently, women were asked about their medication history, including type of medication and frequency of use. For women who completed SOF Visit 8 at home, an interviewer completed the medication history at their residence. Participants were specifically queried as to whether they were taking a given medication for a sleep related problem or condition. A computerized dictionary was used to categorize type of medication from product brand and generic names obtained from containers. Medications were then assigned a therapeutic class based on the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[29] In this analysis, the use of antidepressants, benzodiazepines, and nonbenzodiazepine/nonbarbiturate sedative hypnotics were examined as potential predictors of incident reduced sleep efficiency.

4.3.4.5. Sleep characteristics

Women were asked to report having trouble sleeping due to: pain (not at all vs. one or more times a week); nocturia (not at all vs. one or more times a week); bad dreams (not at all vs. one or more times a week).

4.3.5. Statistical analysis

Descriptive statistics including means, standard deviations for continuous variables, distributions consisting of numbers and percentages for categorical variables were used to summarize the descriptive information of sleep efficiency and predictors of incident reduced sleep efficiency.

Characteristics of the 700 women by status of incident reduced sleep efficiency (no vs. yes) between SOF Visit 8 and Visit 9 were compared using Chi-square or Fisher's exact tests for categorical variables, t-tests for difference in means of continuous variables with normal distributions, and nonparametric Wilcoxon rank-sum tests for continuous variables with skewed distributions.

To determine a final multivariable logistic regression model to examine the associations of potential predictors with incident reduced sleep efficiency, a three-step analytical process was utilized. The first step involved running the base model, which included age, clinical site and the continuous value of sleep efficiency at SOF Visit 8. The second step of the analysis involved adding each potential predictor one at a time to the base model. The significance of a variable in this second step was determined using Benjamin Hochberg false-discovery rate of q-values <0.10. This strategy adjusts for multiple testing and control false discovery rate due to large number of predictors; q-value is considered to be more conservative the p-value alone[30]. The third step was a

multivariable logistic model that included the base model and all predictors that met the q-value < 0.10 criterion. All models included continuous baseline sleep efficiency at SOF Visit 8 in order to make sure that any significant associations between potential predictors and incident reduced sleep efficiency were independent of the variability in baseline sleep efficiency. All logistic regression models were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

To ensure that the most significant variables to explain incident reduced sleep efficiency were accurately identified, a random forest technique was employed. Random forest was originally proposed by Breiman (2001)[7] is a supervised machine learning technique and is an extension of Classification and Regression Trees (CART).[31] In a classification tree, using a value of a correlate, the data set is first split into two subgroups, also called nodes, to maximize the homogeneity of the subgroups. Then, the process is repeated recursively to each node until the nodes can no longer be split. Random forests are ensembles of decision trees that are trained using bootstrapped samples randomly selected from the original dataset to identify and rank most important/predictive features/characteristics that are classifiers of an outcome through the use of variable importance measures(VIM).[7] In building random forests, the data that is not used to create the random forest models is called out-of-bag (OOB) data (also considered as validation/test data) to compute the classification error. The OBB error is averaged over all trees. Smaller OOB error values indicate higher accuracy of the random forest model. VIM of a variable of interest is the difference between the OOB error when a data set is obtained through random permutation of the variable of interest and the OOB error that is obtained

from the original data set. In our analysis, variables with VIM values greater than 2 were considered important, because at a VIM value of 2, there was a large break between variables in terms of VIM values.[32,33]

The Random forest analysis was performed using the Random Forest package in R, version 3.6.2. to classify incident reduced sleep efficiency status among the 700 women and rank the importance of potential predictors. 500 bootstrapped samples were drawn from the data to grow 500 classifications trees and a subset of 5 predictors at each node was used as potential splitting variables. Variables deemed most important in classifying incident reduced sleep efficiency in women from the random forest analysis were compared with the results obtained from the logistic regression to determine the common significant predictors between the two methods.

4.4.Results

Study Population

Baseline demographic and health characteristics of the overall cohort and by absence or presence of incident reduced sleep efficiency are presented in **Table 4.1**. Among the 700 women with normal sleep efficiency at SOF Visit 8 in the analytic cohort, mean (standard deviation [SD]) age was 82.5 years (3.0); 92.0% were non-Hispanic white, and 19.6% reported their health status as fair/poor/very poor. There were 62 women (8.9%) who developed incident reduced sleep efficiency between SOF Visit 8 and Visit 9. Women who developed incident reduced sleep efficiency at SOF Visit 9 had a slower walk speed, and were more likely to report use of benzodiazepine and antidepressants, have at least 1

IADL impairment, depression, hypertension and report poorer health status and trouble sleeping due to pain. (**Table 4.1**).

Demographic and lifestyle predictors of incident reduced sleep efficiency from logistic regression

In the base models, compared to women with normal level of physical activity, women with low level of physical activity at SOF Visit 8 had higher odds of developing incident reduced sleep efficiency at the SOF Visit 9 (odds ratio (OR) = 1.85, 95% confidence interval (CI): 1.03-3.30). In subsequent logistic model, this association was no longer significant with the use of Benjamin Hochberg false-discovery rate of q-value<0.10 to adjust for multiple comparison-corrected significance level. No other demographic/lifestyle factors met the criteria for being a significant predictor of incident reduced sleep efficiency by satisfying both the tradition significance level, alpha of 0.05 and the multiple comparison-corrected significance level. (**Table 4.2**)

Other predictors of incident reduced sleep efficiency from logistic regression

Logistic regression modeling found that development of incident reduced sleep efficiency was significantly associated (q-value <0.10) with antidepressant use (OR=2.96; 95% CI: 1.50-5.85), benzodiazepine use (OR=3.75; 95% CI: 1.69-8.33) and a self-reported diagnosis of hypertension (OR=2.71; 95% CI: 1.43-5.14) (Table 3). After adjustment for age, enrollment site and baseline sleep efficiency, no other measures of general health, mental health, prescription medication use or self-reported sleep characteristics including trouble sleeping due to pain/nocturia/bad dreams were predictive of incident reduced sleep efficiency.

The final logistic regression model

The final multivariable logistic model included age, clinic site, baseline sleep efficiency, antidepressant use, benzodiazepine use and diagnosis of hypertension. The associations of antidepressant use, benzodiazepine use and hypertension with incident reduced sleep efficiency were not substantially altered in magnitude and remained significant in the final multivariable model. In particular, the odds of developing incident reduced sleep efficiency were approximately 3-fold higher among women with history of antidepressant use (adjusted odds ratio (OR) = 3.06, 95% confidence interval (CI): 1.50, 6.25), benzodiazepine use (OR=2.97, 95% CI: 1.30, 6.80), and self-reported hypertension (OR = 2.83, 95% CI: 1.47, 5.45) (**Table 4.4**).

Results from random forest analysis

In random forest analysis, benzodiazepine use (VIM=6.1) was ranked as the most important factor in predicting incident reduced sleep efficiency at SOF Visit 9. The next most important factors ranked by variable importance measures were depressive symptoms (VIM=3.4), health status (VIM=3.4), anxiety (VIM=3.3), and frailty index (VIM=2.1) (**Figure 4.2**).

4.5.Discussion

Reduced sleep efficiency is associated with impaired cognitive function, higher rates of cognitive decline and increased mortality risk in older adults. To date, however, few studies have examined sleep efficiency as an objectively measured outcome. To address this gap, the current study used actigraphy data to calculate sleep efficiency at 2 visits an average of 5.0 years apart in in 700 elderly women enrolled in the Study of

Osteoporotic Fractures, a multi-site, longitudinal, cohort study of community dwelling women 65 years of age or older. This study utilized the traditional logistic regression and random forest technique to examine the determinants of reduced sleep efficiency.

Using logistic regression, several factors were found to be significantly associated with reduced sleep efficiency after adjusting for each other and potential confounders. Our findings suggest that older women with a history of antidepressant use, benzodiazepine use and with self-reported hypertension had approximately 3 times higher odds of developing worsened sleep efficiency. In addition, with random forests, we found that the use of benzodiazepine was the most important factor in predicting incident reduced sleep efficiency, followed by depressive symptoms, self-reported health status, anxiety, and frailty. As stated before, there is a lack of research focusing on reduced sleep efficiency in the older population. To the best of our knowledge, there is one Canadian study that has identified factors associated with poorer sleep efficiency in a population of 2,468 participants, ages 65 and older.[6] Our result regarding the use of benzodiazepine as a significant predictor of incident reduced sleep efficiency in the logistic regression model is somewhat consistent with a finding from the Canadian study, where the use of sleep medication was identified as a significant factor of poorer sleep efficiency (OR=1.82, 95% CI: 1.48, 2.22). However, the other factors associated with poorer sleep efficiency identified in our study are different from those identified in this Canadian study, where the authors concluded that pain, nocturia, and awakening from bad dreams were also associated with poorer sleep efficiency below 80%. Thus, predictors identified in our study add to the list of possible factors associated with reduced sleep efficiency. A plausible

explanation for the discrepancies in results may be the difference in study design (cross sectional study vs. prospective cohort study). In addition, the Canadian study utilized in-home interviews to assess sleep efficiency, which might not be as accurate as objective measures of sleep efficiency measured using actigraphy as performed in our study. To the best of our knowledge, our study in community-dwelling women is the first longitudinal study that examines the determinants of incident reduced sleep efficiency in a population who started out with normal sleep efficiency.

Both traditional logistic regression and random forest found the use of benzodiazepine as the common predictor of developing incident reduced sleep efficiency. This noted association between reduced sleep efficiency and benzodiazepine use confirms what has been known about the adverse events associated with the use of these drugs in older populations. Since the introduction of the Beer's Criteria of Medications to Avoid in the Elderly in the 1970's, benzodiazepines have been identified as drugs of concern.[34] They have been associated with increased risk of falls and fractures, motor vehicle accidents and cognitive impairment/delirium, and rapid eye movement sleep behavior disorder in community-dwelling elderly.[34–37] Our findings strongly suggest that the use of benzodiazepines as indicated by both traditional logistic regression and random forest, and the diagnosis of anxiety (only identified by random forest) for which they may be prescribed, are associated with reduced sleep efficiency. Continued concern about this therapeutic class of drugs is warranted.

The association between reduced sleep efficiency and depression is also noteworthy. Logistic regression identified a history of antidepressant use as a significant

factor, while random forest identified self-reported of depressive symptoms as important. The diagnosis of depression and the subsequent prescription of anti-depressants is widespread in the elderly population[38,39], with serotonin reuptake inhibitors (SSRIs) being the most commonly prescribed this population[40]. Clinical literature suggests a number of adverse effects of antidepressants in the elder population including cognitive impairment and a number of antidepressants are identified as drugs to avoid in the elderly population[34]. A cross sectional study in 2,853 community-dwelling women (ages 71 and older) without evidence of depression attending the SOF Visit 8 found that the use of SSRIs was associated with sleep disturbances including worsened sleep efficiency, longer sleep latency and sleep fragmentation[41]. The result from our longitudinal study on the association of antidepressant use and incident reduced sleep efficiency confirms the finding from this previous study and adds to this literature. Reduced sleep efficiency with its accompanying impaired cognitive function and cognitive decline may compound the adverse effects of antidepressants.

Our results from the random forest technique demonstrated two general and physical health concerns that are associated with reduced sleep efficiency including poorer health status and frailty. There is a known association between frailty and subsequent rating of health status.[42–46] Our study data confirm this general relationship; a higher proportion of women with intermediate or frail status reported having fair/poor/very poor health status. Our analysis demonstrates that both of these characteristics are also associated with reduced sleep efficiency. A study in 3133 community-dwelling older men showed that reduced sleep efficiency was associated with 1.37-fold times higher risk of

developing greater frailty status.[47] Thus, this suggests that there might a bi-directional relationship between frailty and reduced sleep efficiency.

Finally, our results from the logistic models indicated that hypertension was a significant predictor of incident reduced sleep efficiency. The odds ratio (OR=2.83; 95% CI: 1.47,5.45) indicated that history of self-reported hypertension was associated with a nearly 3-fold higher risk of developing incident reduced sleep efficiency. The association of hypertension with sleep related problems including apnea, insomnia, restless leg syndrome and sleep duration above or below the median of 7 to 8 hours per night, has been a subject of published research [48–50]. In general, these published studies examined hypertension as an outcome and sleep parameters as predictors. Our study indicated however, hypertension is a significant factor in the development of incident reduced sleep efficiency. Thus, this suggests that there might a bi-directional relationship between hypertension and sleep health. Further research studies are needed to confirm this association between hypertension and reduced sleep efficiency and explore the mechanism by which these two conditions affect one another.

Our study contributes to the sparse literature on the development of incident reduced sleep efficiency, which is particularly of a great concern for the older populations with high number of comorbid conditions and functional limitations. Our study has several strengths. We used a prospective cohort study with comprehensive assessment of participant characteristics including demographics, lifestyle, general and physical health, sleep characteristics, and prescription drug use factors. We also used repeated objective measures of sleep efficiency through actigraphy, and adjusted for the baseline sleep

efficiency to ensure that the associations between baseline predictors and incident reduced sleep efficiency were independent of baseline sleep efficiency. In addition, we adjusted for multiple comparisons in the analyses involving logistic regression to control for false discovery rate. Furthermore, we also applied random forest, a machine learning technique to confirm, compare and contrast the results to those obtained from the traditional logistic regression. The use of random forest offers many advantages over the traditional logistic regression including its ability to allow the inclusion of correlated data and its potential to explore and find interactions between predictors of incident reduced sleep efficiency independently without any assumptions.[7]

However, this study has limitations. First, the cohort was restricted to older community-dwelling older, primarily white women. Thus, the results might not be generalizable to other populations such as men, younger women, or other more diverse populations. Future studies are warranted to examine longitudinal changes in sleep efficiency in other populations including those residing in institutions such as nursing homes. Second, even though we utilized a longitudinal cohort study and controlled for potential confounders and mediators in our logistic regression, causality of the relationship between predictors and risk of developing incident reduced sleep efficiency cannot be strongly inferred due to the potential for residual confounding. Third, our sample size and the number of events for incident reduced sleep efficiency at follow-up were small. Thus, while we accounted for multiple comparisons in order to reduce the false-positive findings in the analyses involving logistic regression, there might be a chance for false negative findings. Fourth, while we adjusted for baseline characteristics, we did not adjust for

changes in participants' characteristics that might have taken place in between the SOF visits. These changes might be changes in general, physical and mental health, prescription medication use or sleep characteristics, and could further contribute to the development of incident reduced sleep efficiency in older women. Future studies are warranted to determine whether these changes between visits are potential determinants of the development of incident reduced sleep efficiency. Lastly, the random forest technique used in our analysis may have possible shortcomings as it may introduce subjectivity to the analysis, due to the choice of tuning parameters of random forests.[7,51] Correlation between predictors of incident reduced sleep efficiency in the random forests may result in confounding. While random forest ranks predictors in terms of importance to the classification of worsened sleep efficiency, in comparison to logistic regression, random forest is unable to determine the magnitude and direction of the effects of the predictors on worsened sleep efficiency, resulting in a lack of interpretation of results and limiting our understanding of the determinants of worsened sleep efficiency.

In conclusion, our results suggest that the antidepressant use, benzodiazepine use and hypertension may be risk factors for the development of reduced sleep efficiency in women late in life. Results from random forest analysis suggest that in addition to benzodiazepine use as also identified by traditional logistic regression, mental health, physical health and frailty might be predictive of the development of reduced sleep efficiency in older women. Thus, future research is warranted to explore potential biological mechanisms underlying these associations to explain the etiology of reduced sleep efficiency. In addition, future intervention studies/trials are needed to target risk

factors such as depressive symptoms, anxiety, and frailty to determine whether interventions designed to improve these factors would result in improved sleep efficiency. The use of benzodiazepines and antidepressants should be prescribed with caution in older women. Finally, machine learning technique via random forests and other supervised and unsupervised techniques should be used in sleep research as alternative analytical methods to confirm and compare findings.

4.6.Figures and Tables

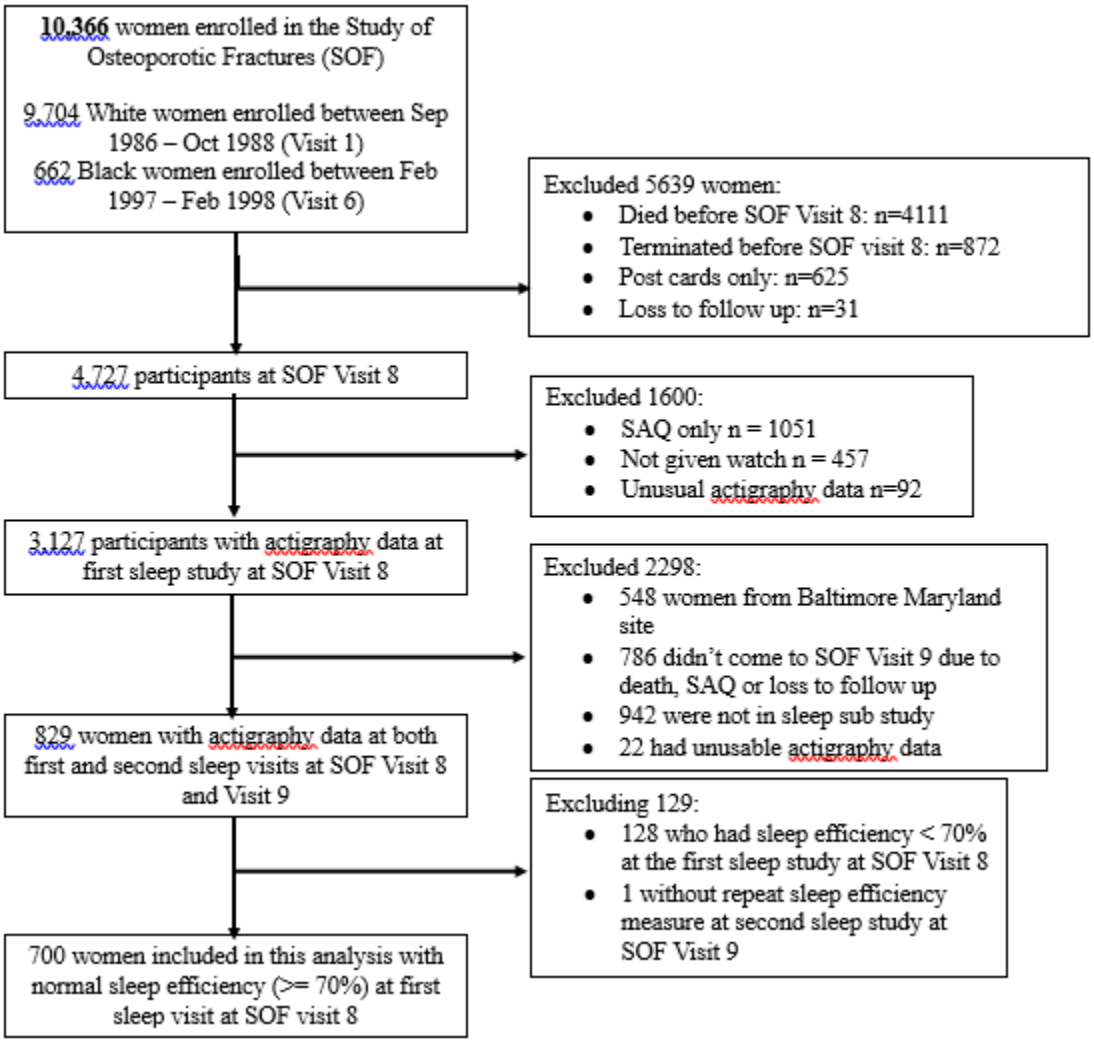

Figure 4.1: Study Flow Chart

Table 4.1: Baseline characteristics for 700 women at SOF Visit 8 by incident reduced sleep efficiency (SE) status

Characteristics	Total N = 700	Normal SE N=638	Incident reduced SE N=62	P-value
Age, mean (SD)	82.5(3.0)	82.5(3.0)	82.8(3.3)	0.4655
SE at sleep visit 1 (%), mean (SD)	83.0(6.0)	83.3(5.9)	79.4(5.5)	<.0001
SE at sleep visit 2 (%), mean (SD)	82.4(9.4)	84.5(6.2)	61.3(10.9)	<.0001
Time in seconds to complete Trails B test(0-180), mean (SD)	114.4(32.2)	113.9(31.4)	120.7(39.8)	0.2394
Short Mini-mental state exam (0-30), mean (SD)	25.0(1.3)	25.0(1.3)	25.0(1.4)	0.8608
Walking speed in meters/second, mean (SD)	0.92(0.22)	0.93(0.22)	0.87(0.22)	0.0563
Race, N(%)				0.3687
White	642(91.7%)	587(92.0%)	55(88.7%)	
Black	58(8.3%)	51(8.0%)	7(11.3%)	
Education, N(%)				0.3307
Less than high school (HS)	115(16.4%)	101(15.8%)	14(22.6%)	
HS	317(45.3%)	289(45.3%)	28(45.2%)	
At least HS	268(38.3%)	248(38.9%)	20(32.3%)	
Smoking status, N(%)				0.6798
Never	434(62.1%)	394(61.9%)	40(64.5%)	
Past/Current	265(37.9%)	243(38.1%)	22(35.5%)	
Alcohol consumption, N(%)				0.0949
0 drinks/week	560(80.0%)	504(79.0%)	56(90.3%)	
1-13 drinks/week	127(18.1%)	121(19.0%)	6(9.7%)	

At least 14 drinks/week	13(1.9%)	13(2.0%)	0(0.0%)	
IADL impairments, N(%)				0.0515
No impairments	398(56.9%)	370(58.0%)	28(45.2%)	
At least 1 impairment	302(43.1%)	268(42.0%)	34(54.8%)	
Depression, N(%)				0.0258
No depression (GDS-15 < 6)	648(92.6%)	595(93.3%)	53(85.5%)	
Depression (GDS-15 >=6)	52(7.4%)	43(6.7%)	9(14.5%)	
Anxiety status, N(%)				0.6466
No anxiety (Goldberge score <= 4)	609(87.1%)	557(87.3%)	52(85.2%)	
Anxiety (Goldberge score >=5)	90(12.9%)	81(12.7%)	9(14.8%)	
Trouble sleeping due to pain, N(%)				0.047
No	474(67.7%)	439(68.8%)	35(56.5%)	
Yes	226(32.3%)	199(31.2%)	27(43.5%)	
Trouble sleeping due to nocturia, N(%)				0.9422
No	81(11.6%)	74(11.6%)	7(11.3%)	
Yes	619(88.4%)	564(88.4%)	55(88.7%)	
Trouble sleeping due to bad dreams, N(%)				0.5379
No	605(86.4%)	553(86.7%)	52(83.9%)	
Yes	95(13.6%)	85(13.3%)	10(16.1%)	
Frailty status, N(%)				0.5689
Robust	216(35.9%)	195(35.5%)	21(41.2%)	
Intermediate (Pre-frail)	302(50.2%)	280(50.9%)	22(43.1%)	

Frail	83(13.8%)	75(13.6%)	8(15.7%)	
Benzodiazepine use, N(%)				0.0011
No	655(93.6%)	603(94.5%)	52(83.9%)	
Yes	45(6.4%)	35(5.5%)	10(16.1%)	
Nonbenzo/nonbarbituate sedative hypnotic use, N(%)				0.4791
No	693(99.0%)	632(99.1%)	61(98.4%)	
Yes	7(1.0%)	6(0.9%)	1(1.6%)	
Antidepressant use, N(%)				0.0013
No	626(89.4%)	578(90.6%)	48(77.4%)	
Yes	74(10.6%)	60(9.4%)	14(22.6%)	
History of hypertension, N(%)				0.0007
No	288(41.1%)	275(43.1%)	13(21.0%)	
Yes	412(58.9%)	363(56.9%)	49(79.0%)	
History of stroke, N(%)				0.5114
No	647(92.4%)	591(92.6%)	56(90.3%)	
Yes	53(7.6%)	47(7.4%)	6(9.7%)	
History of angina(chest pain), N(%)				0.6445
No	622(88.9%)	568(89.0%)	54(87.1%)	
Yes	78(11.1%)	70(11.0%)	8(12.9%)	
History of heart attack, N(%)				0.7782
No	639(91.3%)	583(91.4%)	56(90.3%)	
Yes	61(8.7%)	55(8.6%)	6(9.7%)	
History of COPD/emphysema, N(%)				0.7228
No	630(90.0%)	575(90.1%)	55(88.7%)	

Yes	70(10.0%)	63(9.9%)	7(11.3%)	
History of Parkinsons Disease, N(%)				1
No	698(99.7%)	636(99.7%)	62(100%)	
Yes	2(0.3%)	2(0.3%)	0(0.0%)	
History of rheumatoid arthritis, N(%)				0.8083
No	644(92.0%)	586(91.8%)	58(93.5%)	
Yes	56(8.0%)	52(8.2%)	4(6.5%)	
History of osteoarthritis, N(%)				0.4726
No	436(62.3%)	400(62.7%)	36(58.1%)	
Yes	264(37.7%)	238(37.3%)	26(41.9%)	
History of diabetes, N(%)				0.4508
No	629(89.9%)	575(90.1%)	54(87.1%)	
Yes	71(10.1%)	63(9.9%)	8(12.9%)	
Health status, N(%)				0.0213
Poor/Very Poor/Fair	137(19.6%)	118(18.5%)	19(30.6%)	
Good/Excellent	563(80.4%)	520(81.5%)	43(69.4%)	
Marital status, N(%)				0.707
Not married	482(68.9%)	438(68.7%)	44(71.0%)	
Married	218(31.1%)	200(31.3%)	18(29.0%)	

Table 4.2: Demographics and lifestyle predictors of incident reduced sleep efficiency (models adjusted for age, site and baseline sleep efficiency)

	Incident reduced SE		
	OR(95% CI)	pvalue	q value
Age (years), per SD increase	1.11(0.86,1.43)	0.4181	0.7867
Sleep efficiency (%), per SD increase	0.51(0.39, 0.67)	**<.0001**	**0.0003**
Low physical activity vs. normal level	1.85(1.03,3.30)	**0.0391**	0.2659
Race, Nonwhite vs. white	1.14(0.46,2.85)	0.775	0.9759
Education			
Less than high school vs. at least college	1.58(0.74,3.38)	0.2409	0.63
High school vs. at least college	1.33(0.71,2.47)	0.3743	0.7867
Smoking status, ever vs. never	0.85(0.48,1.50)	0.5753	0.9182

Table 4.3: Health status and disease predictors of incident reduced sleep efficiency (models adjusted for age, site and baseline sleep efficiency)

	Incident reduced SE		
	OR(95% CI)	pvalue	qvalue
IADLs impairment, impaired vs. non-impaired	1.61(0.94,2.75)	0.0852	0.4054
Trails B: Total time ((0-180 sec), per SD increase	1.09(0.82,1.46)	0.5482	0.9182
Short Mini-mental state exam (0-30), per SD increase	1.01(0.77,1.31)	0.95	0.9902
Walk speed (m/s), ?per SD increase	0.80(0.59,1.09)	0.158	0.4884
Depression	1.84(0.82,4.12)	0.1368	0.4651
Anxiety status	1.04(0.48,2.22)	0.9288	0.9902
Trouble sleeping due to pain	1.59(0.92,2.73)	0.0954	0.4054
Trouble sleeping due to nocturia	0.79(0.34,1.86)	0.5941	0.9182
Trouble sleeping due to bad dreams	1.34(0.64,2.79)	0.4396	0.7867
Frailty status			
Prefail vs. Robust	0.71(0.37,1.35)	0.2913	0.7074
Frail vs. Robust	0.96(0.40,2.32)	0.93	0.9902
Antidepressant use	**2.96(1.50,5.85)**	**0.0018**	**0.0195**
Benzodiazepine use	**3.75(1.69,8.33)**	**0.0012**	**0.0195**
Nonbenzo/nonbarbituate sedative hypnotic use	1.51(0.17,13.72)	0.7121	0.9312
History of hypertension	**2.71(1.43,5.14)**	**0.0023**	**0.0195**
History of stroke	1.45(0.58,3.64)	0.4238	0.7867
History of angina(chest pain)	1.19(0.54,2.65)	0.6703	0.9206
History of heart attack	1.09(0.44,2.70)	0.8486	0.9902

History of COPD/emphysema	1.03(0.44,2.40)	0.9502	0.9902
History of rheumatoid arthritis	0.77(0.26,2.26)	0.6366	0.9206
History of osteoarthritis	1.26(0.73,2.17)	0.4042	0.7867
History of diabetes	1.19(0.53,2.67)	0.6769	0.9206
Health status			
Poor/very poor/fair vs. good/excellent	1.68(0.93,3.04)	0.0878	0.4054

Table 4.4. Results from the final multivariable model of the development of incident reduced sleep efficiency in women between SOF Visit 8 (2002-2004) and SOF Visit 9 (2006-2008).

Characteristics	Incident reduced sleep efficiency	
	Odds ratios (95% Confidence interval)	P-value
Age, years (per SD increase)	1.08 (0.83, 1.40)	0.57
Antidepressant use	3.06 (1.50, 6.25)	0.002
Benzodiazepine use	2.97 (1.30, 6.80)	0.01
Self-reported hypertension	2.83 (1.47, 5.45)	0.002

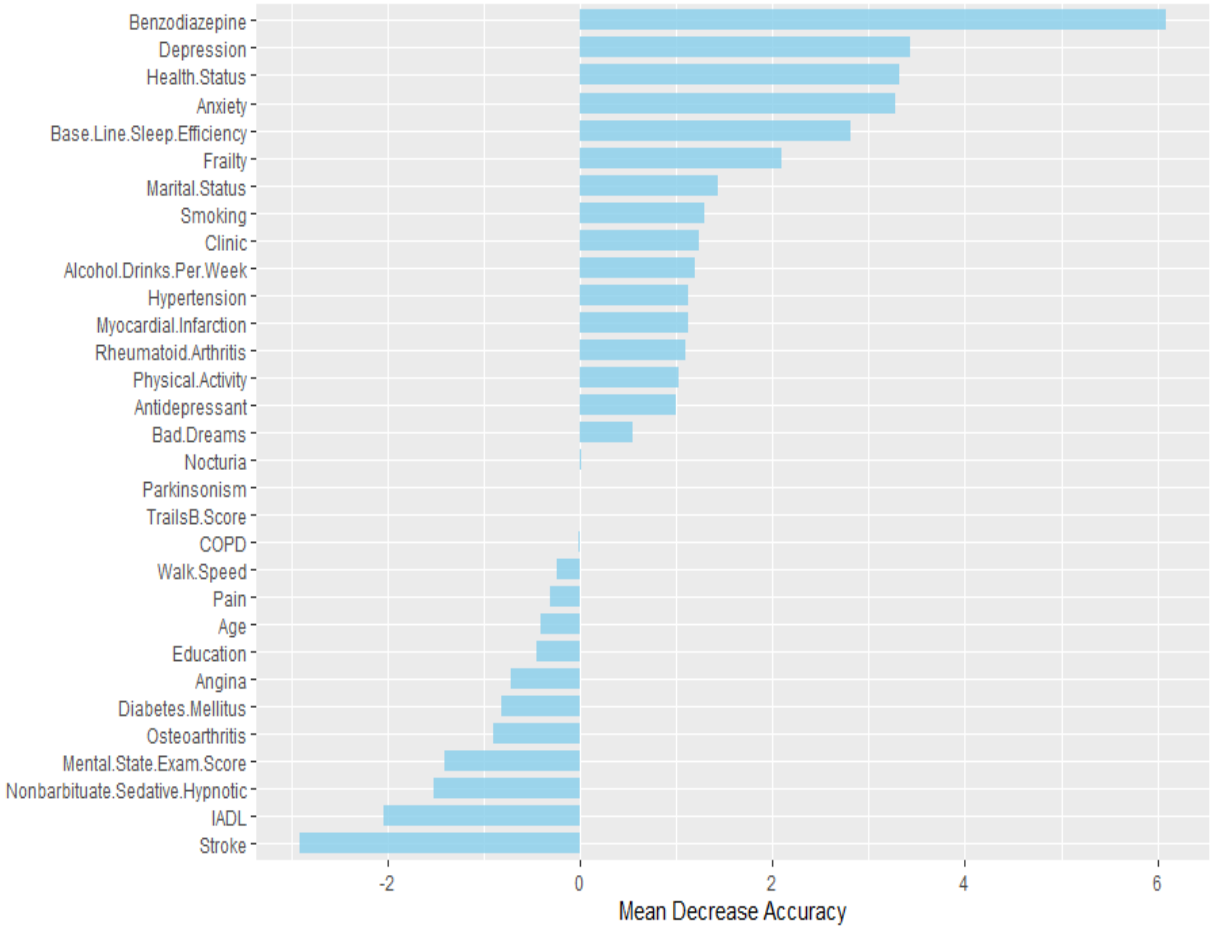

Figure 4.2: Permutation variable importance measures

These measures obtained from the Random forests model are represented by the mean decrease accuracy for each predictor in classifying incident reduced sleep efficiency. The larger the value for mean decrease accuracy due to the exclusion of that variable, the more important the variable in reducing classification error. Variables whose mean decrease accuracy values less than 0 are considered to be non-informative.

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Chapter 5: Manuscript 3

Predictors of incident reduced sleep efficiency in community-dwelling older men

5.1.Overview

Study objectives: To identify potential risk factors for incident reduced sleep efficiency among community-dwelling older men.

Methods: Participants were 487 community-dwelling men (mean age 74.1 [SD=4.6] years) with normal sleep efficiency (SE >=80%) at MrOS Sleep Visit 1 [VS1] (2003-2005) of the Osteoporotic Fractures in Men (MrOS) study, who had repeated measurement of sleep efficiency at the MrOS Sleep Visit 2 [VS2](2009-2012). Sleep efficiency at both time points was measured using overnight polysomnography (PSG). Incident reduced SE was defined by a SE <80% at VS2. Logistic regression was used to estimate the associations of potential predictors with incident reduced sleep efficiency in minimally and fully adjusted models. Variable importance measures obtained from random forest analysis were used to rank predictors most important in predicting incident reduced sleep efficiency.

Results: 262 (53.8%) men developed incident reduced sleep efficiency between VS1 and VS2. Men with higher baseline sleep efficiency had 31% lower odds of developing incident reduced sleep efficiency based on age and clinical site adjusted logistic regression models (adjusted odds ratio (OR) = 0.69, 95% confidence interval (CI): 0.57,

0.83) per 1 SD increase in baseline sleep efficiency. However, measures of general health, general mental health, prescription medication use or sleep characteristics (including trouble sleeping due to pain, nocturia, or bad dreams) were not found to be predictive of incident reduced sleep efficiency after adjustment for age, enrollment site and baseline sleep efficiency. On the other hand, random forest models identified depressive symptoms as the most important factor in predicting incident reduced sleep efficiency in men, followed by cognitive function, nocturia, diabetes, weekly alcohol consumption and baseline sleep efficiency.

Conclusions: Machine learning techniques such as random forests could be valuable in identifying novel risk factors for adverse sleep outcomes such as incident reduced sleep efficiency. Depressive symptom, cognitive function, nocturia, diabetes, consumption of alcoholic drinks and baseline sleep efficiency may be important factors for the development of reduced sleep efficiency in older men.

Keywords: incident reduced sleep efficiency, polysomnography, older men, logistic regression, machine learning, random forests.

5.2.Introduction

Sleep efficiency, defined as the percentage of time in bed spent sleeping, is a key measure of sleep health and has been shown to decrease with advancing age.[1–3] Sleep efficiency below 80% is associated with increased mortality risk in older adults, and has been proposed as the primary parameter to be assessed and targeted to promote optimal

sleep health in older adults.[4] Furthermore, reduced sleep efficiency is associated with higher rates of cognitive decline in older men[5].

While some studies have examined sleep efficiency as a predictor of adverse health outcomes and conditions, there is a paucity of research that has considered sleep efficiency as an outcome measure. A Canadian study of 2468 community-dwelling men and women 65 years of age and older (mean age = 73.7 [SD = 6.1] found that pain, nocturia, sleep medication use and awakening from bad dreams were predictive of having a sleep efficiency below 80%.[6] However, the study had several limitations including a cross-sectional design and use of interviews to assess self-reported efficiency rather than an objective measure like polysomnography (PSG) or actigraphy.

Given that reduced sleep efficiency is associated with increased risk of adverse outcomes in older adults, longitudinal research is warranted to identify predictors of the development of incident reduced sleep efficiency. Identifying the determinants of objectively measured reduced sleep efficiency in the elderly population is particularly important for the design of potential interventions aimed at improving sleep health among this population and to inform evidence-based recommendations regarding prevention and treatment of age-related impairment in sleep health. For example, the development of incident reduced sleep efficiency may be a cause, marker or consequence of developing adverse health conditions and diseases.

The objective of the present longitudinal study was to identify factors associated with incident reduced sleep efficiency in U.S. older community-dwelling men enrolled in the Osteoporotic Fractures in Men (MrOS) Study. Analyses were performed using

logistic regression and a newer machine learning technique, random forest. Like logistic regression, random forest analysis can be used to solve classification problems[7]. In the last 15 years random forest analysis has been used in diverse fields including computational biology, personalized medicine and engineering.[8–13]

5.3.Methods

5.3.1. Study population

We studied participants enrolled in the MrOS study, a prospective cohort study of 5994 community-dwelling older men, aged ≥65 years. Men were recruited between March 2000 to April 2002 from six US cities: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA. Details of the MrOS study design and recruitment have been described elsewhere.[14,15]

Recruitment for Outcomes of Sleep disorders in Older Men (VS1) study occurred from December 2003 to March 2005 among the pool of 5605 active participants (Figure 1). Among these men, 150 were not eligible for the VS1 study because they were receiving treatment for sleep apnea or snoring, 1997 were invited but declined participation, and 323 were not asked to participate because the study recruitment goal had been met. Thus, a total of 3135 (57%) men agreed to participate in the VS1 (exceeding the recruitment goal of 3000 men).

The second MrOS Sleep Visit (VS2) was completed between 11/10/2009 and 3/15/2012; 2911 men who remained active in the MrOS study and had usable PSG data from the VS1 were eligible to be contacted to participate in the VS2. All active minority participants with usable PSG data from VS1 were contacted for participation in VS2; non-

minority participants were contacted in random order for enrollment until a study recruitment goal of 1000 participants was met. Of the 2911 men that remained active in VS1, follow-up was not expected for 64 (2.2%); 856 (29.4%) refused further study participation; 538 (18.5%) died prior toVS2; 37 (1.3%) terminated; 54 (1.9%) were not eligible and 307 (10.6%) were not contacted. Recruitment goals for the VS2 study were exceeded with a total of 1055 enrolled participants. Among these 1055 men, 1026 had usable PSG data at both VS1 and VS2. We excluded 539 men who had sleep efficiency <80% at the VS1. The remaining 487 men are included in the present analysis (**Figure 5.1**).

5.3.2. PSG

In-home sleep studies were completed using a level 2 PSG (Safiro, Compumedics, Inc.®, Melbourne, Australia). The PSG recordings were obtained within one month of the clinic visit (mean 6.9 ± 15.8 days from visit), with 78% of recordings gathered within one week of the clinic visit. The recordings included C3/A2 and C4/A1 electroencephalograms, bilateral electrooculograms and a bipolar submental electromyogram to determine sleep stage, thoracic and abdominal respiratory inductance plethysmography to determine respiratory effort, airflow (by nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry (SpO2) for measuring oxygen saturation, lead I EKG,body position (mercury switch sensor), and bilateral tibialis leg movements (piezoelectric sensors). Centrally-trained and certified staff performed home visits to set up the unit, verify the values of the impedances for each channel, confirm calibration of position sensors and note any problems encountered during set-up, similar to the protocol used in the Sleep Heart Health Study.[16] Staff returned the next morning to collect the equipment and download the

data to the Central Sleep Reading Center (Cleveland, OH) to be scored by certified research polysomnologists blinded to all other data.

For VS2, approximately every 6 months a test sample of 10 to 20 records were scored to document inter-and intra-scorer reliability by the primary scorer (937) assigned to MrOS (May 2010, January 2011, October 2012-November 2012). Intra-class correlation coefficients were generated for these reliability assessments for key sleep variables. Two certified scorers from the VS1study participated in training and follow-up review of the first 100 VS2 studies. PSG data quality was deemed excellent, with a failure rate of less than 4%; more than 70% of the assessments were graded as excellent or outstanding quality.

5.3.3. Outcome variable

Sleep efficiency was defined as the percentage of time spent sleeping during the entire in-bed interval. Incident reduced sleep efficiency was calculated from PSG results at two time points. A man was classified as having incident reduced sleep efficiency (yes/no) if he had normal sleep efficiency (SE >= 80%) at VS1 and reduced sleep efficiency (SE < 80%) at VS2.

5.3.4. Predictors of incident reduced sleep efficiency

5.3.4.1. Demographic and lifestyle factors

At the VS1, men completed questionnaires on demographics including age (continuous), race (white vs. others). Highest education obtained (years) was collected at MrOS baseline visit. In addition, participants reported lifestyle factors including smoking

history (yes/no), and alcohol use (number of drinks/week). Physical activity level was accessed using the Physical Activity Scale for the Elderly (PASE).[17]

5.3.4.2. General and physical health

Participants were asked to report health status (excellent/good vs. fair/poor/very poor) and a physician diagnosis (yes/no) of selected medical conditions including hypertension, stroke, angina, myocardial infarction, chronic obstructive pulmonary disease (COPD), Parkinson disease, cataracts, rheumatoid arthritis, osteoarthritis, and diabetes mellitus. Usual gait speed was measured using the 6-meter walk speed in meter/second. The presence of impairment (yes/no) in Instrumental Activities of Daily Living (IADL) was determined by asking the men if they had difficulty in doing the following five instrumental activities of daily living: heavy housework, walking 2 to 3 blocks, climbing 10 stairs, shopping for groceries or clothing, and preparing meals on his own.[18,19] A man was considered to have an IADL impairment (yes vs.no) if he reported difficulty on at least one activity. Frailty was defined using the SOF index[20] and was identified if data was available for at least two of the following three components: 1) weight loss of ≥5% between MrOS baseline visit and VS1, regardless of whether a man was trying to lose weight or not; 2) unable to stand up from a chair five times without using the arms; and 3) reporting poor energy by having an answer of "No" to the question "Do you feel full of energy?" on the Geriatric Depression Scale. A man was considered robust if he had none of these three components, intermediate (pre-frail) if he had 1 component and frail if he had at least 2 components.

5.3.4.3. Mental health

Depressive symptoms (yes/no) were assessed using the Geriatric Depression Scale (GDS-15)[21]; a participant with GDS-15 score ≥6 was considered to have depression. A man was considered to have significant anxiety symptoms (yes/no) if his Goldberg anxiety score was ≥5[22]. Global cognitive function was measured using the Mini-Mental State Examination (3MS), scored from 0 to 100, with higher 3MS scores representing better cognitive functioning.[23] Executive function (mental skills that include working memory, flexible thinking, and self-control) was also assessed using the Trails B test, with shorter Trails B time spent on completing the test representing better cognitive functioning.[24]

5.3.4.4. Prescription drug use

Men were asked to bring all current (defined as daily or almost daily use in the 30 days preceding the examination) prescription and nonprescription medications with them to VS1. Subsequently, participants were asked about their medication history, including type of medication and frequency of use. Participants were specifically queried as to whether they were taking a medication for a sleep related problem or condition. A computerized dictionary was used to categorize type of medication from product brand and generic names obtained from containers. Medications were then assigned a therapeutic class based on the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[25] In this analysis, the use of antidepressants, benzodiazepines, and nonbenzodiazepine/nonbarbiturate sedative hypnotics were considered as candidate predictor variables.

5.3.4.5. Self-reported sleep characteristics

Men were asked to report having trouble sleeping due to: pain (not at all vs. one or more times a week); nocturia (not at all vs. one or more times a week); and bad dreams (not at all vs. one or more times a week).

The institutional review boards on human research approved the study at each institution. All participating men provided informed consent.

5.3.5. Statistical analysis

Descriptive statistics (means, standard deviations for continuous variables; distributions consisting of numbers and percentages for categorical variables) were used to summarize the descriptive information of sleep efficiency and predictors of incident reduced sleep efficiency. Participants' characteristics by status of incident reduced sleep efficiency between VS1 and VS2 were compared using Chi-square or Fisher's exact tests for categorical variables, t-tests for difference in means of continuous variables with normal distributions, and nonparametric Wilcoxon rank-sum tests for continuous variables with skewed distributions.

To determine a final multivariable logistic regression model to examine the associations of potential predictors with incident reduced sleep efficiency, a three-step analytical process was utilized. The first step was performing the base model, which included age, clinical site and the continuous value of sleep efficiency at VS1. The second step of the analysis was adding each potential predictor one at a time to the base model and determining its significance, using the Benjamin Hochberg false-discovery rate of q-values <0.10. This strategy adjusts for multiple testing and controls for the false discovery rate due to a large number of predictors; q-value is considered to be more

conservative the p-value alone[26]. The third step was a multivariable logistic model that included the independent variables in the base model and all predictors that met the q-values < 0.10 criterion. All models included continuous baseline sleep efficiency at VS1 to ensure that any significant associations between potential predictors and incident reduced sleep efficiency were independent of the variability in baseline sleep efficiency. All logistic regression models were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Random forest technique was also employed to identify to further investigate incident reduced sleep efficiency in this population of older men. Random forest, as originally proposed by Breiman (2001),[7] is a supervised machine learning technique and is an extension of Classification and Regression Trees (CART).[27] In a classification tree, using a value of a correlate, the data set is first split into two subgroups, also called nodes, to maximize the homogeneity of the subgroups. Then, the process is repeated recursively to each node until the nodes can no longer be split. Random forests are ensembles of decision trees that are trained using bootstrapped samples randomly selected from the original dataset to identify and rank the most important/predictive features/characteristics that are classifiers of an outcome through the use of variable importance measures(VIM).[7] In building random forests, the data not used to create the random forest models is called out-of-bag (OOB) data (also considered as validation/test data) and is used to compute the classification error. The OOB error is averaged over all trees. Smaller OOB error values indicate higher accuracy of the random forest model. VIM of a variable of interest is the difference between the OOB error when a data set is obtained through random permutation

of the variable of interest and the OOB error that is obtained from the original data set. A large break or drop in VIM values is usually used to rankvariables important to the classification problems in random forests. [28,29]

The Random forest analysis was performed using the Random Forest package in R[30], version 3.6.2. to classify incident reduced sleep efficiency status among men included in the analytical cohort and rank the importance of potential predictors. In our analysis, 500 bootstrapped samples were drawn from the data to grow 500 classifications trees; a subset of 5 predictors at each node was used as potential splitting variables. Variables deemed most important in classifying incident reduced sleep efficiency in men from the random forest analysis were contrasted with the results obtained from the logistic regression.

5.4.Results

Study Population

Baseline demographic and health characteristics of the overall cohort and by absence or presence of incident reduced sleep efficiency are presented in **Table 5.1**. Among the 487 men with normal sleep efficiency at VS1 in the analytic cohort, mean age was 74.1 years ±4.6 years; 88.1% were non-Hispanic white; 9.0% reported their health status as fair/poor/very poor; and 85.4% completed at least college education. Incident reduced sleep efficiency between VS1 and VS2 developed in 262 men (53.8%). There were no statistically significant differences in demographics and lifestyle factors; measures of general, physical and mental health; or use of antidepressants, benzodiazepines, and nonbenzodiazepine/nonbarbiturate sedative hypnotics between men who developed

incident reduced sleep efficiency at VS2 and those whose sleep efficiency remained normal. Nonetheless, men who developed incident reduced sleep efficiency at VS2 were more likely at baseline to have lower sleep efficiency and report having history of osteoarthritis, have trouble sleeping due to nocturia, and less likely to report having chest pain (**Table 5.1**).

Predictors of incident reduced sleep efficiency from logistic regression

Men with higher baseline sleep efficiency had 31% lower odds of developing incident reduced sleep efficiency based on age and clinical site adjusted logistic regression models (adjusted odds ratio (OR) = 0.69, 95% confidence interval (CI): 0.57, 0.83) per 1 SD increase in baseline sleep efficiency. No demographic or lifestyle factors met the criteria for being a significant predictor of incident reduced sleep efficiency by satisfying either or both the traditional significance level, alpha of 0.05 and the multiple comparison-corrected significance level (**Table 5.2**). After adjustment for age, enrollment site and baseline sleep efficiency, no predictors of general health, mental health, prescription medication use or sleep characteristics (including trouble sleeping due to pain, nocturia, or bad dreams) were predictive of incident reduced sleep efficiency (Table 5.2).

Since no predictors met the stringent criterion of Benjamin Hochberg false-discovery rate of q-values <0.10, no final logistic regression model was selected to predict incident reduced sleep efficiency in older men in our analytical cohort.

Results from random forest analysis

Figure 5.2 represents the output of all variables for random forest technique. Based on the decision rule criterion generally applied in the random forest technique, a VIM value of 2.5, where there was a large break in VIM values for predictors, was chosen as the cut off-point to identify important variables in predicting incident reduced sleep efficiency in men. Using 2.5 as the cut-off point for VIM value, there were five variables deemed most important in predicting incident reduced sleep efficiency in men. Depression as defined by a GDS score less than 6 (VIM=4.9) was ranked as the most important factor in predicting incident reduced sleep efficiency in community-dwelling older men at VS2. The next most important factors ranked by variable importance measures were cognitive function as indicated by trails B scores (VIM=4.6), nocturia (VIM=3.8), diabetes (VIM=3.3), alcoholic drinks per week (VIM=3.1) and baseline sleep efficiency (VIM=2.53) (**Figure 5.2**).

5.5.Discussion

While lower sleep efficiency has been associated with higher risks of cognitive decline and mortality in the aged population, few studies have examined the development of incident reduced sleep efficiency as an objectively measured outcome in older men. To address this gap, the current study used objective sleep measures obtained through polysomnography to evaluate sleep efficiency for 486 men at two sleep visits, who were enrolled in the Study of Osteoporotic Fractures in Men, a multi-site, longitudinal, cohort study of community dwelling men 65 years of age or older. In this study, the determinants of reduced sleep efficiency in community-dwelling older men were examined using the traditional logistic regression and random forest technique.

Our study indicated that for one standard deviation increase in baseline sleep efficiency, the odds of developing incident reduced sleep efficiency in community-dwelling older men was 0.69 times lower, after adjusting for age and clinical sites. However, no factors in logistic models other than baseline sleep efficiency were found to be significantly associated with reduced sleep efficiency after adjusting for age and study enrollment site and controlling for the false discovery rate. Potential reasons for the null findings using logistic regression include the lack of signals between incident reduced sleep efficiency and predictors and a small sample size, hence inadequate power in our study. The lack of power might be especially relevant for potential risk factors with low prevalence, such as several of the medical conditions including depression. In contrast, using random forest technique, we found that depression was the most important factor in explaining incident reduced sleep efficiency in community-dwelling older men at VS2, followed by trails B test scores, nocturia, diabetes, alcoholic drinks per week and baseline sleep efficiency. To the best of our knowledge, there is only one Canadian study that has identified factors associated with poorer sleep efficiency in a population of 2468 participants, ages 65 and older.[6] Our result regarding nocturia as one of the important predictors of incident reduced sleep efficiency is consistent with a finding from the Canadian study. However, the other factors associated with poorer sleep efficiency identified in our study differ from those identified in the Canadian study, where the authors concluded that pain, nocturia, and awakening from bad dreams were also associated with poorer sleep efficiency below 80%. Reasons for the discrepancies in results may be due to statistical noise and differences in study design (cross sectional study vs. prospective cohort

study). In addition, the Canadian study utilized in-home interviews to assess sleep efficiency, rather than the objective measure of sleep efficiency measured through PSG as performed in our study. Furthermore, our study calculated sleep efficiency from PSG at two visits thus allowing us to longitudinally identify factors that can predict a participant with normal sleep efficiency at baseline will subsequently develop incident reduced sleep efficiency. Thus, predictors identified using random forest in our study add to the list of potential predictors for reduced sleep efficiency in older men.

While traditional logistic regression did not find any independent predictor of incident reduced sleep efficiency, random forest identified depressive symptom score dichotomized at the cutoff value for a diagnosis of depression as the most important variable. Literature on the association of depression and sleep efficiency is sparse and has documented inconsistent findings[31–33]. Paudel et al examined the association of risk of depression and sleep efficiency using both subjective and objective measures of sleep efficiency parameters in 2510[32] and in 3051 community-dwelling older men[33] respectively, who were enrolled in the MrOS study. Paudel et al. found out that there was no association between depression and sleep efficiency after adjusting for potential confounders in both studies. A study by Sukegawa et al. in 4682 elderly Japanese population concluded that participants with self-reported sleep efficiency < 75% had 1.3 times higher odds of developing depression compared to those with normal sleep efficiency (OR=1.3; 95% CI: 1-1.7).[31] Our results from the traditional logistic regression is consistent with the lack of association between sleep efficiency and depression as reported by Paudel et al. In contrast, our results suggesting an association between depression and lower probabilities of

developing reduced sleep efficiency from the random forest technique is not in agreement with the finding from the Japanese study by Sukegawa et al. though the latter study modeled depression as the outcome and reduced sleep efficiency as a predictor variable. Together, these findings suggest that the relationship between reduced sleep efficiency and depression is a complex one that might be bidirectional by nature and not thoroughly understood as suggested by other studies.[32,34,35] Further investigations on the association between depressive symptoms and risk of reduced sleep efficiency in other populations are warranted to confirm or refute our findings and to explore mechanisms underlying any association.

The association between reduced executive function as manifested by longer time to complete the Trails B test and risk of reduced sleep efficiency as suggested by findings from random forest analysis is also noteworthy. While cognitive function assessed by measures of global or executive function was not an independent predictor of reduced sleep efficiency in logistic regression (OR = 1.11; 95% CI = 0.91,1.35), reduced executive function (but not global cognition) was the second most important variable in predicting incident reduced sleep efficiency in the random forest analysis as indicated by the partial dependency plot where probabilities of developing incident reduced sleep efficiency increased with higher Trails B test scores. Previous cross-sectional studies have shown that poor sleep is associated with worsened cognitive function.[36–38] Additionally, prior literature has reported associations of reduced sleep efficiency with impaired cognitive function (including global measurement using Mini-Mental State Examination (MMSE), Trail Making B Test, verbal fluency, encoding and retaining verbal material from the

Consortium to Establish a Registry for Alzheimer's Disease test battery and subjective cognitive functioning from self-reported questionnaires) in older men and women. [38, 39] A cross-sectional study by Biddle et al. showed that men (50 years and older) with poor objective sleep efficiency as measured using actigraphy had a 4.15 higher odds of developing impaired executive function (OR=4.15; 95% CI: 1.35-12.69).[41] The result from the random forest of our longitudinal study on the association between reduced executive function and incident reduced sleep efficiency in context of previous studies reporting associations of impaired sleep with lower executive function suggests the presence of a bidirectional association between sleep efficiency and executive function.

Results from random forest identified nocturia as third most important variable in predicting incident reduced sleep efficiency. Nocturia has been shown to be one of the causes of sleep disturbances, especially in the older populations.[42] Clinical literature also suggests that nocturia is associated with impaired functioning, worsened quality of life, health and productivity.[43–45] Longitudinal studies on the association of incident reduced sleep efficiency and nocturia in older men are scarce. One Canadian study conducted by Desjardins et al. concluded that compared to older men (65 years and older) without nocturia, those with nocturia had a 2.26 times higher odds of developing reduced sleep efficiency as measured by sleep report.[6] Thus the result from our longitudinal study on the association of nocturia and incident reduced sleep efficiency is in agreement with the finding from this previous study.

Our results from the random forest technique indicates that diabetes may be an important predictor of reduced sleep efficiency in community-dwelling older men. While

sleep disturbances and lack of sleep have been shown to be associated with diabetes[46,47], the association between sleep efficiency as measured objectively using PSG and diabetes has not been well examined. A recent cross-sectional study by Yan et al concluded that poor sleep efficiency as measured using polysomnography was associated with diabetes in 4737 community-dwelling older adults (mean age = 63.6 ± 11.0 years), who were without sleep-disordered breathing and enrolled in the Sleep Heart Health Study (SHHS) (OR=1.89; 95% CI: 1.19-3.02).[48] In addition, clinical research has indicated that the cause-and-effect relationship between diabetes and sleep is a complex one that still needs further investigations. Barone et al. argued the association between diabetes and sleep is a cycle, where sleep disorders may lead to the development of diabetes or diabetes itself might lead to sleep disorders when diabetes is associated with poor metabolic control. [49] Furthermore, a cross-sectional study in 162 patients in Thailand found that lower sleep efficiency measured by actigraphy was associated with lower cognitive function (measured by using the Thai version of the Montreal Cognitive Assessment) in patients with prediabetes and type 2 diabetes.[50] Hence, cognitive impairment together with diabetes might exacerbate reduced sleep efficiency.

Finally, our results from random forest analysis indicated that the number of alcoholic drinks per week was an important predictor of incident reduced sleep efficiency. While the literature on this association between sleep efficiency and alcoholic drinks is scarce, the association of alcohols with sleep related problems including sleep-disordered breathing (SDB), sleep apnea, insomnia, and periodic leg movements has been a subject of published research. [51–55] In general, these published studies examined the potential

pathways and mechanisms by which alcohol intake affects the quality of sleep. Given these negative effects of alcohols on sleep, it is possible that high number of alcoholic drinks per week would lead to reduced sleep efficiency in older men, among whom the prevalence of SDB and sleep apnea is high. Furthermore, alcohol often used as a sedative agent can interact with prescription and over-the-counter drugs that are prescribed to older adults. The consumption of alcoholic drinks may exacerbate cognitive impairment, which might further lead to reduced sleep efficiency. Given our hypothesis on the possible association between incident reduced sleep efficiency and alcoholic consumptions, it was interesting that our findings on this association were opposite of what we had expected. The use of alcoholic drinks was found to be protective of developing incident reduced sleep efficiency in community-dwelling older men in our study (OR = 0.78; 95 % CI: 0.51,1.20 for 1-13 drinks/week vs. None and OR = 0.60; 95% CI: 0.28,1.31 for at least 14 drinks/week vs. None). Partial dependence plot from random forests also indicated similar marginal effects of alcoholic drinks on reduced sleep efficiency, where the probabilities of developing incident reduced sleep efficiency are slightly higher for men who did not consume alcoholic drinks vs. 1-13 drinks/week and at least 14 drinks per week. A plausible explanation for this finding might be due to enrollment of healthy men in the MrOS study and that former drinkers (who may have abstained from alcohol due to health conditions) along with never drinkers are included in the group of men not currently consuming alcoholic drinks.

Our study has several strengths. First, our study contributes to the sparse literature on the development of incident reduced sleep efficiency in community-dwelling older men.

Second, this study used a prospective cohort study with comprehensive assessments of participant characteristics including demographics, lifestyle, measures of general and physical health, sleep characteristics, and prescription drug use. Third, our study obtained repeated objective measures of sleep efficiency through PSG, and adjusted for the baseline sleep efficiency to ensure that the associations between baseline predictors and incident reduced sleep efficiency were independent of baseline sleep efficiency. Fourth, we controlled for false discovery rate using the Benjamin Hochberg method in logistic regression to deal with the issues of multiple comparisons. Finally, we also applied random forest, a machine learning technique to confirm, compare and contrast the results to those obtained from the traditional logistic regression. The use of random forest offers many advantages over the traditional logistic regression including its ability to allow the inclusion of correlated data and its potential to explore and find interactions between predictors of incident reduced sleep efficiency independently without any assumptions.[7]

Despite the strengths, this study has limitations. First, there is lack of power in this study due to small size of the study population and low prevalence of some candidate predictors. Thus, the findings of this study should be interpreted with caution. Second, our study population consisted of relatively well-functioning mostly white, community-dwelling older men. Hence, the results of this study might not be generalizable to other populations such as men in younger age groups, or other more diverse populations, and cannot be applied to women or older adults residing in institutions. Future research studies are warranted to examine longitudinal changes in sleep efficiency in other populations. Third, even though we utilized a longitudinal cohort study and controlled for potential

confounders and mediators in our logistic regression, causality of the relationship between predictors and risk of developing incident reduced sleep efficiency cannot be strongly inferred due to the potential for residual confounding. Fourth, even though we adjusted for baseline characteristics, we did not adjust for changes in participants' characteristics that might have taken place in between the MrOS sleep visits 1 and 2. These changes might be changes in general, physical and mental health, prescription medication use or sleep characteristics, and could further contribute to the development of incident reduced sleep efficiency in older men. Furthermore, the random forest technique used in our analysis may have possible shortcomings as it may introduce subjectivity to the analysis, due to the choice of tuning parameters of random forests.[7,56] Results obtained from random forests may be confounded by the correlations between predictors included in the model to classify incident reduced sleep efficiency between MrOS sleep visits 1 and 2. Finally, while random forest models rank predictors in terms of importance to the classification of worsened sleep efficiency, in comparison to logistic regression, they are unable to determine the magnitude and direction of the effects of the predictors on worsened sleep efficiency, resulting in a lack of interpretation of results and limiting our understanding of the determinants of worsened sleep efficiency.

In conclusion, our results from random forest analysis suggest that depressive symptom, cognitive function, nocturia, diabetes, and alcoholic drinks per week may be factors of importance in explaining the development of reduced sleep efficiency in older men. Thus, future research is warranted to explore potential biological mechanisms underlying these associations to explain the etiology of reduced sleep efficiency in men.

Finally, results from random forests and logistic regression were different and thus should be interpreted with caution due to the aforementioned limitations of this study and of the statistical methods.

5.6.Figures and Tables

Figure 5.1: Study Flow Chart

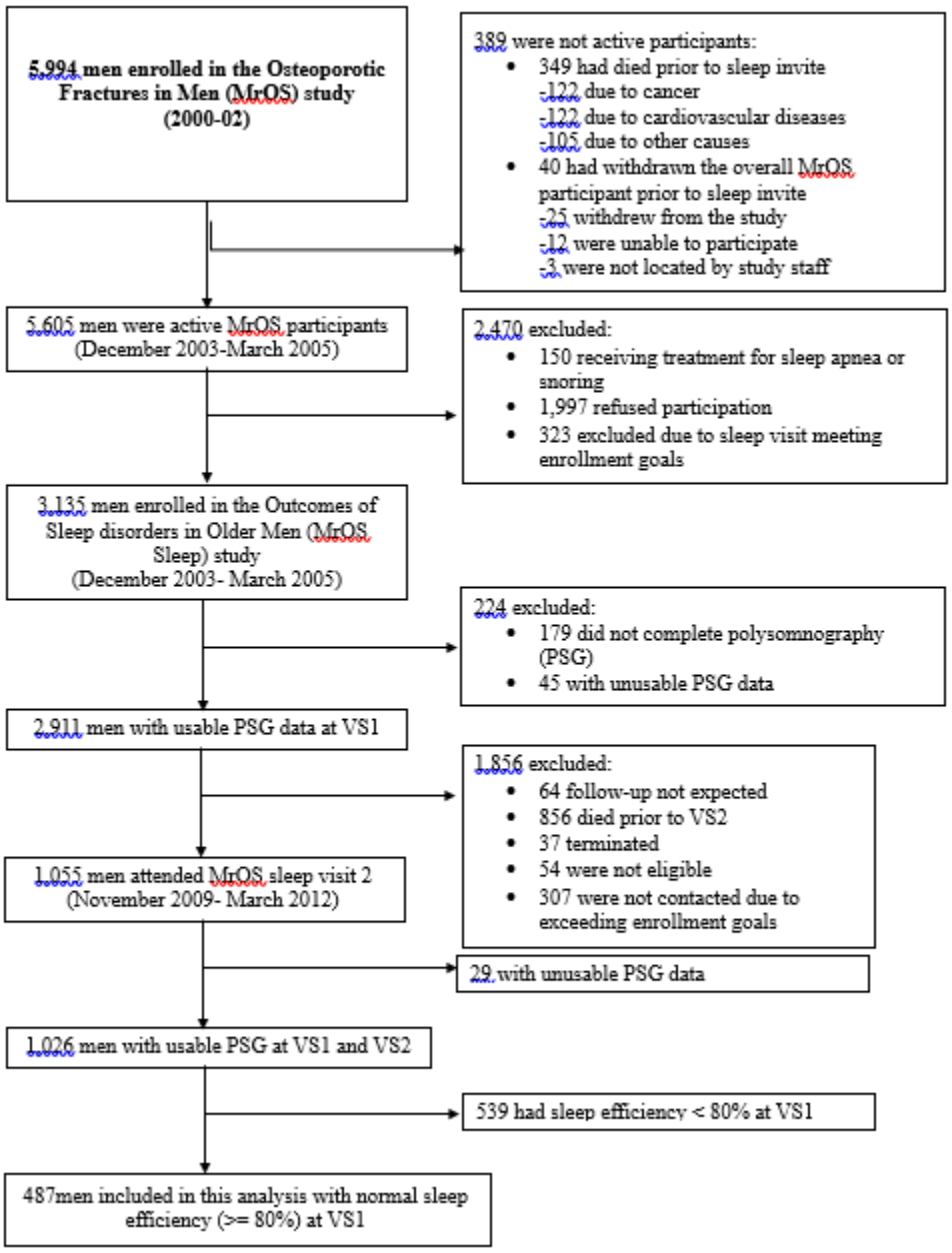

Table 5.1: Baseline characteristics for 487 men at VS1 by incident reduced sleep efficiency (SE) status

Characteristics	Total N=487	Normal SE N=225	Incident reduced SE N=262	P-value
Age, mean (years)	74.1(4.6)	73.8(4.6)	74.4(4.6)	0.14
Sleep efficiency at VS1 (%), mean (SD)	86.5(4.3)	87.3(4.4)	85.8(4.0)	<.0001
Sleep efficiency at VS2 (%), mean (SD)	77.2(11.6)	86.6(4.2)	69.2(9.7)	<.0001
PASE Score, mean (years)	160.2(67.6)	159.5(69.4)	160.9(66.2)	0.83
Time in seconds to complete Trails B test (0-300), mean (SD)	103.1(40.1)	101.0(40.3)	105.0(39.8)	0.28
Short Mini-mental state exam (0-100), mean (SD)	94.3(4.4)	94.4(4.4)	94.3(4.4)	0.72
Walking speed in meters/second, mean (SD)	1.2(0.21)	1.21(0.21)	1.19(0.22)	0.20
Race, N(%)				0.74
Others	58(11.9%)	28(12.4%)	30(11.5%)	
White	429(88.1%)	197(87.6%)	232(88.5%)	
Education, N(%)				0.44
Less than high school (HS)	15(3.1%)	9(4.0%)	6(2.3%)	
HS	56(11.5%)	28(12.4%)	28(10.7%)	
At least college	416(85.4%)	188(83.6%)	228(87.0%)	
Smoking status, N(%)				0.23

Never	222(45.6%)	96(42.7%)	126(48.1%)	
Past/Current	265(54.4%)	129(57.3%)	136(51.9%)	
Alcohol consumption/week, N(%)				0.25
0 drinks/week	134(27.8%)	55(24.8%)	79(30.4%)	
1-13 drinks/week	312(64.7%)	147(66.2%)	165(63.5%)	
At least 14 drinks/week	36(7.5%)	20(9.0%)	16(6.2%)	
IADLs impairment, N(%)				0.43
No impairments	429(88.1%)	201(89.3%)	228(87.0%)	
At least 1 impairment	58(11.9%)	24(10.7%)	34(13.0%)	
Depression, N(%)				0.40
No depression (GDS-15 < 6	473(97.1%)	217(96.4%)	256(97.7%)	
Depression (GDS-15 >=6)	14(2.9%)	8(3.6%)	6(2.3%)	
Anxiety status, N(%)				0.84
No anxiety (Goldberge score <= 4)	461(94.9%)	212(94.6%)	249(95.0%)	
Anxiety (Goldberge score >=5)	25(5.1%)	12(5.4%)	13(5.0%)	
Trouble sleeping due to pain, N(%)				0.60
No	345(70.8%)	162(72.0%)	183(69.8%)	
Yes	142(29.2%)	63(28.0%)	79(30.2%)	
Trouble sleeping due to nocturia, N(%)				0.07
No	38(7.8%)	23(10.2%)	15(5.7%)	

Yes	449(92.2%)	202(89.8%)	247(94.3%)	
Trouble sleeping due to bad dreams, N(%)				0.75
No	369(75.8%)	169(75.1%)	200(76.3%)	
Yes	118(24.2%)	56(24.9%)	62(23.7%)	
Lack of energy, N(%)				0.12
No	313(64.5%)	152(68.2%)	161(61.5%)	
Yes	172(35.5%)	71(31.8%)	101(38.5%)	
Frailty status, N(%)				0.79
Robust	258(53.8%)	122(55.5%)	136(52.3%)	
Intermediate (Pre-frail)	192(40.0%)	85(38.6%)	107(41.2%)	
Frail	30(6.3%)	13(5.9%)	17(6.5%)	
Benzodiazepine use, N(%)				0.94
No	470(96.5%)	217(96.4%)	253(96.6%)	
Yes	17(3.5%)	8(3.6%)	9(3.4%)	
Nonbenzo/nonbarbituate sedative hypnotic use, N(%)				0.80
No	473(97.1%)	219(97.3%)	254(96.9%)	
Yes	14(2.9%)	6(2.7%)	8(3.1%)	
History of hypertension, N(%)				1.00
No	277(56.9%)	128(56.9%)	149(56.9%)	

Yes	210(43.1%)	97(43.1%)	113(43.1%)	
History of stroke, N(%)				0.58
No	474(97.3%)	218(96.9%)	256(97.7%)	
Yes	13(2.7%)	7(3.1%)	6(2.3%)	
History of angina(chest pain) , N(%)				0.03
No	418(85.8%)	185(82.2%)	233(88.9%)	
Yes	69(14.2%)	40(17.8%)	29(11.1%)	
History of heart attack, N(%)				0.43
No	422(86.7%)	192(85.3%)	230(87.8%)	
Yes	65(13.3%)	33(14.7%)	32(12.2%)	
History of COPD/emphysema, N(%)				1.00
No	474(97.3%)	219(97.3%)	255(97.3%)	
Yes	13(2.7%)	6(2.7%)	7(2.7%)	
History of Parkinsons Disease, N(%)				0.50
No	485(99.6%)	225(100%)	260(99.2%)	
Yes	2(0.4%)	0(0%)	2(0.8%)	
History of cataracts, N(%)				0.65
No	289(59.3%)	136(60.4%)	153(58.4%)	
Yes	198(40.7%)	89(39.6%)	109(41.6%)	
History of rheumatoid arthritis, N(%)				0.96

No	457(93.8%)	211(93.8%)	246(93.9%)	
Yes	30(6.2%)	14(6.2%)	16(6.1%)	
History of osteoarthritis, N(%)				0.05
No	365(74.9%)	178(79.1%)	187(71.4%)	
Yes	122(25.1%)	47(20.9%)	75(28.6%)	
History of diabetes, N(%)				0.55
No	433(88.9%)	198(88.0%)	235(89.7%)	
Yes	54(11.1%)	27(12.0%)	27(10.3%)	
Health status, N(%)				0.73
Poor/Very Poor/Fair	39(8.0%)	17(7.6%)	22(8.4%)	
Good/Excellent	448(92.0%)	208(92.4%)	240(91.6%)	
History of cerebrovascular disease, N(%)				0.53
No	454(93.2%)	208(92.4%)	246(93.9%)	
Yes	33(6.8%)	17(7.6%)	16(6.1%)	
History of peripheral arterial disease, N(%)				0.73
No	453(93.8%)	211(94.2%)	242(93.4%)	
Yes	30(6.2%)	13(5.8%)	17(6.6%)	
Antidepressant use, N(%)				0.62
No	447(91.8%)	208(92.4%)	239(91.2%)	
Yes	40(8.2%)	17(7.6%)	23(8.8%)	

Table 5.2: Demographics and lifestyle predictors of incident reduced sleep efficiency in community-dwelling older men (models adjusted for age, site and baseline sleep efficiency)

	Incident reduced SE		
	OR(95% CI)	P value	q value
Age (years), per SD increase	1.18(0.98,1.43)	0.0895	0.8055
Sleep efficiency (%), per SD increase	0.69(0.57,0.83)	**0.0001**	**0.0036**
PASE Score, per SD increase	1.09(0.90,1.31)	0.396	0.8672
Race, Nonwhite vs. white	0.89(0.49,1.61)	0.7043	0.9462
Education			
Less than high school vs. at least college	0.53(0.18,1.58)	0.254	0.8672
High school vs. at least college	0.77(0.42,1.43)	0.4095	0.8672
Smoking status, ever vs. never	0.76(0.53,1.11)	0.1555	0.8672
Alcohol consumption/week			
1-13 drinks/week vs. None	0.78(0.51,1.20)	0.2569	0.8672
At least 14 drinks/week vs. None	0.60(0.28,1.31)	0.1984	0.8672

Table 5.3: Health status and disease predictors of incident reduced sleep efficiency in community-dwelling older men (models adjusted for age, site and baseline sleep efficiency)

	Incident reduced SE		
	OR(95% CI)	pvalue	qvalue
IADLs impairment, impaired vs. non-impaired	1.09(0.61,1.95)	0.7705	0.9462
Trails B: Total time (0-300 sec), per SD increase	1.11(0.91,1.35)	0.2924	0.8672
Teng 3MS (0 to 100), per SD increase	0.97(0.80,1.18)	0.7764	0.9462
Walk speed (m/s)	0.86(0.71,1.06)	0.1516	0.8672
Depression	0.56(0.18,1.70)	0.3039	0.8672
Anxiety status	0.86(0.37,1.97)	0.7194	0.9462
Trouble sleeping due to pain	1.02(0.68,1.53)	0.9237	0.9471
Trouble sleeping due to nocturia	1.60(0.80,3.21)	0.1858	0.8672
Trouble sleeping due to bad dreams	0.92(0.60,1.42)	0.708	0.9462

Lack of energy	1.19(0.81,1.77)	0.3775	0.8672
Frailty status			
Prefail vs. Robust	1.03(0.70,1.52)	0.8845	0.9471
Frail vs. Robust	1.03(0.46,2.31)	0.9448	0.9471
Antidepressant use	1.21(0.61,2.38)	0.5913	0.9462
Benzodiazepine use	1.04(0.38,2.84)	0.9471	0.9471
Nonbenzo/nonbarbituate sedative hypnotic use	1.13(0.37,3.46)	0.8326	0.9471
History of hypertension	0.92(0.64,1.34)	0.6647	0.9462
History of stroke	0.73(0.24,2.27)	0.5883	0.9462
History of angina(chest pain)	0.52(0.31,0.89)	0.0172	0.3096
History of heart attack	0.78(0.45,1.35)	0.3786	0.8672
History of COPD/emphysema	0.78(0.25,2.48)	0.6785	0.9462
History of cataracts	0.95(0.65,1.40)	0.7885	0.9462
History of rheumatoid arthritis	1.03(0.47,2.24)	0.9432	0.9471

History of osteoarthritis	1.57(1.02,2.41)	0.0422	0.5064
History of diabetes	0.76(0.42,1.35)	0.3486	0.8672
Health status, good/excellent vs. poor/very poor/fair	0.89(0.45,1.78)	0.7465	0.9462
History of cerebrovascular disease	0.83(0.40,1.73)	0.621	0.9462
History of peripheral arterial disease	1.15(0.53,2.51)	0.7244	0.9462

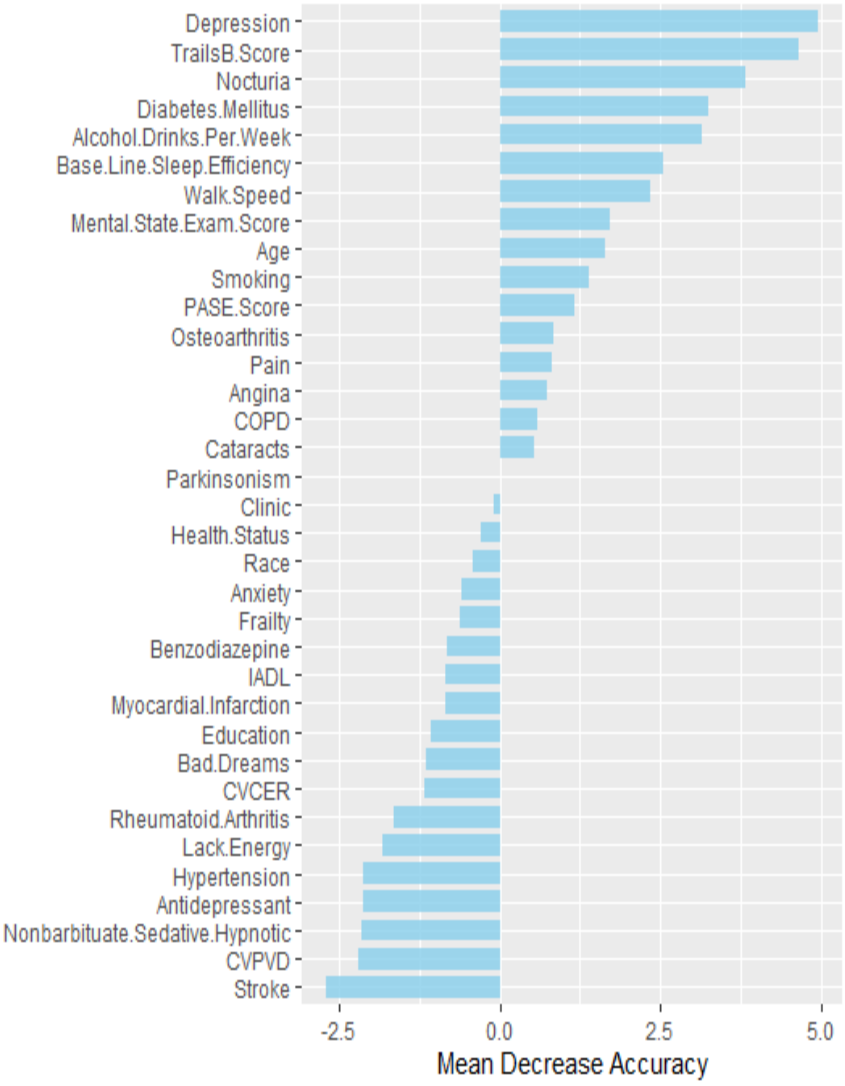

Figure 5.2: Permutation variable importance measures

These measures obtained from the Random forests model are represented by the mean decrease accuracy for each predictor in classifying incident reduced sleep efficiency. The larger the value for mean decrease accuracy due to the exclusion of that variable, the more important the variable in reducing classification error. Variables whose mean decrease accuracy values less than 0 are considered to be non-informative.

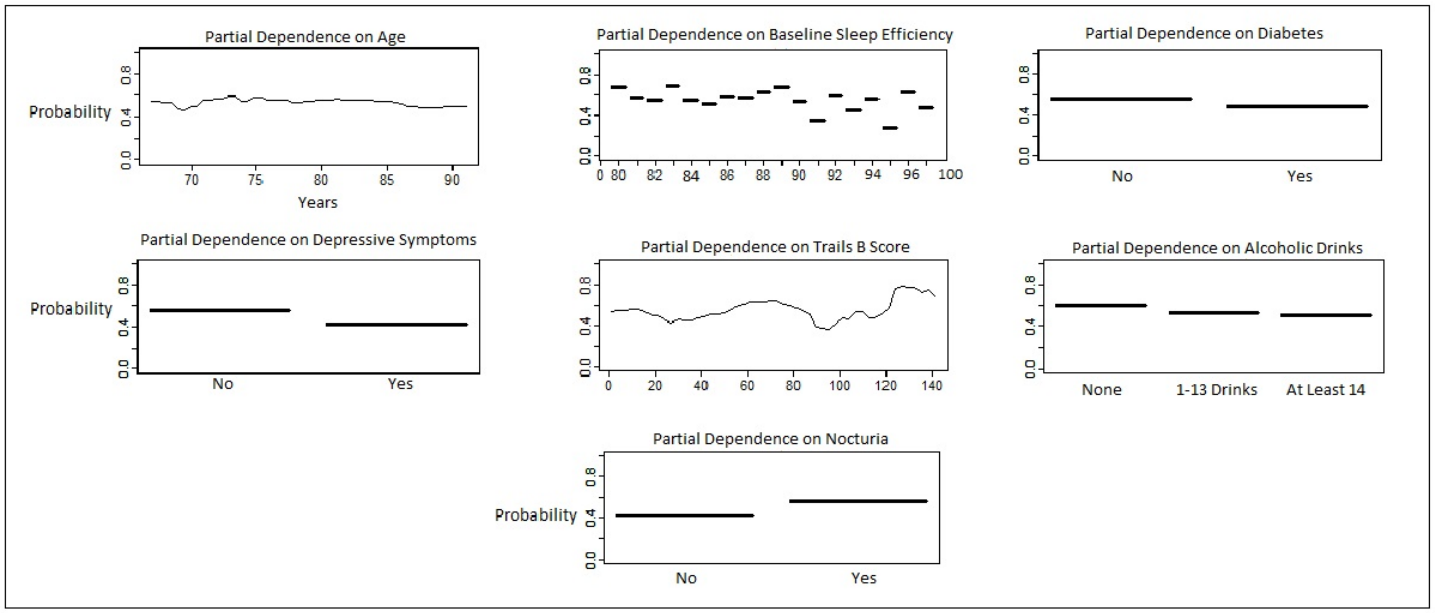

Figure 5.3: Partial Dependence Plots

This shows the marginal effects of the independent variables on incident reduced sleep efficiency.

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Chapter 6: Discussion

6.1.Summary of study results

6.1.1. Summary of the first-manuscript results

This manuscript examined the associations of sleep-disordered breathing (SDB) with subsequent healthcare costs and utilization, including inpatient and post-acute care facility stays, among community-dwelling older men. The study described included 1316 men with a mean age of 76.1 years (SD=5.7). Data was obtained by linking Medicare claims data with cohort data from the Outcomes of Sleep Disorder in Older Men (MrOS). Primary SDB measures including apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) were collected using in-home level 2 polysomnography. Incident healthcare costs and utilization were determined from claims data in the subsequent 3-year period post MrOS sleep visit.

Approximately 40.2% of the men had at least one hospitalization in the 3-year period. Results from logistic regression suggested that compared to those without sleep apnea (AHI <5/hour), men with moderate to severe sleep apnea (AHI ≥15/hour) had a higher odds of all-cause hospitalization (odds ratio [OR] adjusted for age and site 1.43, 95% confidence interval [CI] 1.07-1.90). This association was slightly attenuated after further adjustment for traditional prognostic factors including education, body mass index, comorbid medical conditions, and health status (OR=1.36; 95% CI 1.01-1.83). Similar associations were observed for Oxygen Desaturation Index (ODI). However, measures of

SDB were not related to subsequent healthcare costs (total or outpatient) or odds of post-acute skilled nursing facility stay.

Results from this manuscript suggest that SDB is associated with higher risk of hospitalization (but not with total healthcare costs) in community-dwelling older men. This association is not entirely explained by a greater number of cardiovascular or medical conditions among those men with SDB. Future studies are needed to evaluate the association between SDB and healthcare costs and utilization among other patient populations and to evaluate the effect of treatment of SDB on these measures of healthcare burden.

6.1.2. Summary of the second-manuscript results

The objective of this manuscript was to examine potential risk factors for incident reduced sleep efficiency among community-dwelling women in the 9th decade of life using traditional logistic regression and the machine learning technique, random forest. The study included a population of 700 women (mean age 82.5 [SD=3.0] years) with normal sleep efficiency (SE >=70%) at SOF Visit 8 exam (2002-2004) of the Study of Osteoporotic Fractures (SOF), who had repeated measurement of sleep efficiency at the SOF Visit 9 exam (2006-2008).

Approximately 9% of the women meeting study inclusion criteria developed incident reduced sleep efficiency between SOF Visits 8 and 9. Results from the multivariable logistic regression models suggested that the odds of developing incident

reduced sleep were higher among women self-reporting a history of antidepressant use (adjusted odds ratio (OR) = 3.06, 95% confidence interval (CI): 1.50, 6.25), benzodiazepine use (OR=2.97, 95% CI: 1.30, 6.80), and hypertension (OR = 2.83, 95% CI: 1.47, 5.45). Random forest identified the use of benzodiazepine as the most important factor in predicting incident reduced sleep efficiency, followed by depressive symptoms, health status, anxiety, and frailty. Both random forest and logistic regression identified benzodiazepine use as a common determinant of incident reduced sleep efficiency.

The results from logistic regression and random forest suggest that a history of antidepressant use, benzodiazepine use, self-reported hypertension, depressive symptoms, health status, anxiety and frailty may be risk factors for the development of reduced sleep efficiency in women late in life. Future studies are warranted to explore potential biological mechanisms underlying these associations. In addition, machine learning via random forests and other supervised and unsupervised techniques should be used in sleep research to compare findings

6.1.3. Summary of the third-manuscript results

The third manuscript generated from this research focused on the potential risk factors for incident reduced sleep efficiency among community-dwelling older men. The study included 487 community-dwelling men (mean age 74.1 [SD=4.6] years) with normal sleep efficiency (SE >=80%) at MrOS Sleep Visit 1 [VS1] (2003-2005) of the Osteoporotic

Fractures in Men Study (MrOS), who had repeated measurement of sleep efficiency at the MrOS Sleep Visit 2 [VS2](2009-2012).

The results indicated that 53.8% of the men developed incident reduced sleep efficiency between VS1 and VS2. Results from logistic regression suggested that the odds of developing incident reduced sleep efficiency were 0.69 times lower with 1 SD increase in baseline sleep efficiency (adjusted odds ratio (OR) = 0.69, 95% confidence interval (CI): 0.57, 0.83) in the age and site- adjusted model; measures of general health, general mental health, prescription medication use or sleep characteristics (including trouble sleeping due to pain, nocturia, or bad dreams) were not found to be predictive of incident reduced sleep efficiency after adjustment for age, enrollment site and baseline sleep efficiency. On the other hand, random forest models identified depressive symptoms as the most important factor in predicting incident reduced sleep efficiency in men, followed by cognitive function, nocturia, diabetes, weekly alcohol consumption and baseline sleep efficiency.

The results reported in this manuscript suggest that baseline sleep efficiency might be a potential risk factor for incident reduced sleep efficiency in men. Future studies are needed to further examine this association with the hope for targeting possible interventions to improve sleep efficiency for better sleep health. In addition, machine learning techniques such as random forests may be valuable in identifying risk factors for adverse sleep outcomes such as incident reduced sleep efficiency. Depressive symptom, cognitive function, nocturia, diabetes, consumption of alcoholic drinks and baseline sleep

efficiency may be risk factors for the development of reduced sleep efficiency in older men. Caution is warranted regarding the interpretations of the potential relationship between depression and incident reduced sleep efficiency from the random forest in this small population of community-dwelling men in this study.

6.2.Implications of the dissertation

The research efforts reported in this dissertation examined the association of sleep-disordered breathing with subsequent measures of health care utilization and costs in U.S. community-dwelling older men, and broadened our understanding of the determinants of incident reduced sleep efficiency in both community-dwelling older men and women. The findings of this dissertation have several clinical implications.

First, the findings from this dissertation suggest that SDB, as manifested by higher AHI, ODI or OSA, was associated with a higher risk of all-cause hospitalizations even after adjusting for potential confounders and prognostic indicators. In addition, the findings also suggested that measures of SDB were not related to total healthcare costs or to a risk of post-acute skilled nursing facility stays. Given the association of SDB and risk of all-cause hospitalizations found in this longitudinal study of older community-dwelling men, clinicians and researchers may be better able to identify individuals with increased risks of all-cause hospitalizations using the reported findings. Even though the analyses reported in this dissertation did not find a significant association between measures of SDB and subsequent total healthcare costs and utilizations in community dwelling-older men, future

studies are warranted to investigate the effects of treatments of SDB on all-cause hospitalizations and subsequently on healthcare costs and utilization. In addition, findings from the first manuscript also indicated that men with moderate to severe nocturnal hypoxemia had lower outpatient costs compared to men without hypoxemia in the full multivariable model. This may be a spurious result due to random chance alone or to the numerous comparisons performed. Hence, while treatment of sleep apnea may yield health benefits, our data suggest that lower healthcare costs will likely not be among those benefits.

Second, findings from the second manuscript reported in this dissertation suggest that older women with a history of antidepressant use, benzodiazepine use and with self-reported hypertension had approximately 3 times higher odds of developing worsened sleep efficiency. In addition, with random forests, we found that the use of benzodiazepine was the most important factor in predicting incident reduced sleep efficiency, followed by depressive symptoms, self-reported health status, anxiety, and frailty. As explained earlier in the second manuscript, benzodiazepines have been identified as drugs of concern, especially in the elderly. Our findings on the effects of benzodiazepines on the development of sleep efficiency in older women further validate what has been found in the literature and could inform clinicians to be cautious when prescribing this therapeutic class of drugs to older women. In contrast to the finding on the association of use of benzodiazepines and the development of incident reduced sleep efficiency in women, the impact of the use benzodiazepines on the development of incident reduced sleep efficiency

was not demonstrated in our study of community-dwelling men in the third manuscript. While it is possible that the difference might be due to many reasons including chance findings, statistical noise, and perhaps related to underlying study populations, there could also be potential reasons for the difference in response in sleep efficiency to the use of benzodiazepines in elderly women versus elderly men. Further understanding of the difference of the effects of benzodiazepines by gender might be a fruitful area of research.

The final manuscript presented in this dissertation indicated that for a one standard deviation increase in baseline sleep efficiency, the odds of developing incident reduced sleep efficiency in community-dwelling older men decreases by a factor of 0.69, after adjusting for age and clinical sites. However, in the logistic models no factors other than baseline sleep efficiency were found to be significantly associated with reduced sleep efficiency after adjusting for age and study enrollment site and controlling for the false discovery rate. Future intervention studies aiming to improve sleep efficiency among older men population are warranted. Findings from the random forest analysis suggest that depressive symptoms, cognitive function, nocturia, diabetes, and alcoholic drinks per week may be factors for the development of reduced sleep efficiency in older men. Caution is needed when interpreting these results from the random forest, which could be due to chance findings or due to our small sample size and the limitations of random forests as pointed out in the discussion of the third manuscript.

It is worth noting that sleep efficiency used in this dissertation was measured objectively using actigraphy and polysomnography. While literature suggests that these

two methods have moderate correlations for sleep efficiency, it is not clear that these measures provide the same measures of sleep efficiency.

6.3.Strengths of the research presented in this dissertation

The research analyses reported in this dissertation have several strengths. First, this research employed two prospective cohort studies with comprehensively assessed participant characteristics. The first manuscript utilized published and validated methodology to compute standardized healthcare costs and ascertain healthcare utilization from administrative data, linkage of cohort participants to their Medicare claims data. Potential confounding and mediating factors were considered.

Second, the second and the third manuscripts of this dissertation contribute to the sparse literature on the development of incident reduced sleep efficiency in elderly women and men, which is of a great concern for the older populations with high number of comorbid conditions and functional limitations. To examine factors related to the development of incident reduced sleep efficiency, prospective cohort studies (SOF and MrOS) were used. These prospective cohort studies included comprehensive assessments of participant characteristics including demographics, lifestyle, general and physical health, sleep characteristics, and prescription drug use factors.

Third, unlike other studies of sleep efficiency, the analyses for this dissertation used repeated objective measures of sleep efficiency through actigraphy and polysomnography (PSG), and adjusted for the baseline sleep efficiency to ensure that the associations between

baseline predictors and incident reduced sleep efficiency were independent of baseline sleep efficiency.

Fourth, multiple comparisons were employed in the analyses involving logistic regression to control for false discovery rate. Furthermore, random forest, a machine learning technique was applied to confirm and compare the results to those obtained from the traditional logistic regression. The use of random forest offers many advantages over the traditional logistic regression including its ability to allow the inclusion of correlated data and its potential to explore and find interactions between predictors of incident reduced sleep efficiency independently without any assumptions.

6.4.Limitations of the research presented in this dissertation

This dissertation has several limitations. First, the first manuscript only included healthy community-dwelling older men, with few non-Caucasian participants. Thus, the results might not be generalizable to women, others from different racial or ethnic groups, older men in poorer health, or those residing in other institutions like nursing homes. Second, data on total healthcare and outpatient costs, hospital and SNF stays were only available for those men enrolled in Medicare FFS, but not for those enrolled in Medicare Advantage.

Third, particularly for the second and third manuscripts, even though prospective, longitudinal cohort studies were used and potential confounders and mediators were adjusted for in logistic regression models, causality of the relationship between predictors

and risk of developing incident reduced sleep efficiency in older women and men cannot be strongly inferred due to the potential for residual confounding.

Fourth, sample sizes and number of events for incident reduced sleep efficiency at follow-up for both studies in men and women in the second and third manuscripts at follow-up. Thus, while multiple comparisons were used to control for false-positive findings in the analyses involving logistic regression, there might be a chance for false negative findings.

Fifth, while the second and third manuscripts adjusted for baseline characteristics, changes in participants' characteristics that might have taken place in between the SOF/MrOS visits were not included. The omission of these variables was due to the fact that they were not collected during the SOT/MrOS studies. Other changes in between MrOS/SOF visits might be changes in general, physical and mental health, and prescription medication use or sleep characteristics, and could further contribute to the development of incident reduced sleep efficiency in older women.

Sixth, while objective measures of sleep efficiency were used: actigraphy in the second manuscript and polysomnography in the third manuscript due to logistic reasons when the sleep studies were conducted for MrOS/SOF, it is not clear whether measures of sleep efficiency from actigraphy and polysomnography in fact can be used interchangeably.

Finally, despite the advantages the random forest technique offers, it also has possible shortcomings as it may introduce subjectivity to the analysis due to the choice of tuning parameters of random forests as discussed in the second and third manuscripts. Correlations between predictors of incident reduced sleep efficiency in the random forests may result in confounding. While random forest ranks predictors in terms of importance to the classification of worsened sleep efficiency, in comparison to logistic regression, random forest is unable to do hypothesis testing when the magnitude and direction of the effects of the predictors on worsened sleep efficiency are of interest. This resulted in a lack of interpretation of results and limiting our understanding of the determinants of worsened sleep efficiency.

6.5.Recommendations for future research

This dissertation examined the association of sleep-disordered breathing with subsequent measures of health care utilization and costs in U.S. community-dwelling older men. In addition, this dissertation also broadened our understanding of the determinants of incident reduced sleep efficiency in community-dwelling older men and women. However, several research questions have emerged from this dissertation. First, future studies are needed to confirm findings and to further investigate associations of SDB and other outcomes, such as long-term nursing home placement. Additional research efforts to examine the association between SDB and healthcare costs and utilizations in older women and other racial or ethnic groups, men in poorer health or those residing in nursing homes

are needed to further elucidate these associations. Second, further research is needed to investigate the incremental costs of SDB in populations with underlying commodities such as diabetes and CVDs. Third, the dissertation noted that there was a significant and pronounced effect of the use of benzodiazepines on sleep efficiency in elderly women but not in elderly men. Last, further research utilizing much larger sample sizes including both elderly men and women and using preferably the same method of objectively measuring sleep efficiency is needed to explore the potential difference in the effects of benzodiazipines on sleep efficiency by gender.

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