Sleep and Cardiometabolic Disease

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Dedication

This dissertation is dedicated to my grandmother, Esther Ogilvie. Thank you for your support and understanding. I hope I am lucky enough to live a long full life like you.

Abstract

Sleep is a universal part of human physiology yet sleep disturbances such as short sleep duration and sleep apnea are common. Cardiovascular disease and its risk factors are also common, and it has been hypothesized that sleep disturbances may be linked to greater cardiovascular risk. This dissertation reports on epidemiological associations of sleep duration with eating behaviors and obesity, as well as associations between obstructive sleep apnea and cardiovascular events.

Using data from Project EAT, the first manuscript examines the association between several self-reported sleep indices and problematic eating behaviors in young adults. Late sleep timing was most consistently associated with poor eating behaviors, while fewer associations were found for other sleep indices.

In the second manuscript, data from the Multi-Ethnic Study of Atherosclerosis were used to evaluate the association between actigraphy-measured sleep indices and adiposity in older adults. Those sleeping less than 5 hours per night had higher BMIs, larger waists, and more kilograms of body fat than those who slept 7-8 hours a night. Those with low sleep efficiency and high sleep variability also had greater adiposity.

Using data from the Sleep Heart Health Study, the third manuscript examines the relationship between daytime sleepiness and obstructive sleep apnea in relation to incident coronary heart disease and stroke. We found no significant interaction or synergy, indicating that measuring both sleep characteristics provides little additional information about cardiovascular disease incidence.

In the fourth manuscript, we examine the association between diagnosed sleep apnea and atherosclerotic cardiovascular disease among patients with atrial fibrillation in the MarketScan administrative databases. Counterintuitively, we found that sleep apnea was associated with reduced risk of stroke and myocardial infarction, potentially due to error in the measurement of the exposure.

This dissertation explores the epidemiology of sleep and cardiometabolic disease, including its clinical and public health implications.

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Abbreviations

AF – atrial fibrillation
AHI – apnea-hypopnea index
APAP – autoadjusting/autotitrating positive airway pressure
BMI – body mass index
BPAP – bilevel positive airway pressure
BRFSS – Behavioral Risk Factor Surveillance System
CAC – coronary artery calcium
CARDIA – Coronary Artery Risk Development in Young Adults study
CHD – coronary heart disease
C-IMT – carotid intima-media thickness
CPAP – continuous positive airway pressure
CVD – cardiovascular disease
ECG – electrocardiogram
EOG - electrooculogram
EEG - electroencephalogram
EMG - electromyogram
HDL – high-density lipoprotein
HDPS – high-dimensional propensity scores
LDL – low-density lipoprotein
MI – myocardial infarction
MESA – Multi-Ethnic Study of Atherosclerosis
NHIS – National Health Interview Study
NREM – nonrapid eye movement sleep
OSA – obstructive sleep apnea
PSQI – Pittsburgh Sleep Quality Index
RDI – respiratory disturbance index
REM – rapid eye movement sleep
RERA – respiratory effort-related arousals
RERI – relative excess risk due to interaction
SHHS – Sleep Heart Health Study
WASO – wake after sleep onset

Chapter 1: Overview of sleep and health

Sleep is a universal aspect of human physiology that is essential for health. Sleep health is defined in terms of five dimensions: duration, continuity or efficiency, timing, alertness/sleepiness, and satisfaction/quality.[1] Due to its importance, there is now a Healthy People 2020 topic devoted to sleep health. Its objectives include increasing treatment of sleep apnea, decreasing drowsy driving related car crashes, and increasing hours of sleep for both adults and high school students.[2]

An estimated 25-30% of American adults suffer from sleep problems[3] such as sleep apnea, insomnia, narcolepsy, restless leg syndrome, or sleep deficiency.[4] On the individual level, sleep deprivation/disorders have been associated with cardiovascular risk factors and diseases, loss of productivity, increased injuries, and billions of dollars in direct medical costs.[5] On a larger scale, disasters such as Three Mile Island, Chernobyl, and the grounding of the Exxon Valdez oil tanker have been attributed to individual errors stemming from fatigue, sleep loss, or night shift failures. [6]

Because sleep apnea and short sleep duration are highly prevalent, have adverse health effects, and are included in Healthy People 2020, they will be the primary focus of this dissertation. Since children and adolescents have different sleep needs, this dissertation will focus on adults.

Introduction to sleep duration

Sleep duration refers to the amount of sleep an individual gets in a day. Definitions for research vary, but for adults short sleep is often defined as <6 or <7 hours,

while long sleep often refers to >8 or 9 hours. Currently, the American Academy of Sleep Medicine and the Sleep Research Society recommends that adults should sleep at least 7 hours a night for optimal health.[7] However, Behavioral Risk Factor Surveillance System (BRFSS) data from 2014 demonstrated that 33.8% of Americans were not meeting this recommendation.[8] From 1985 to 2012, mean sleep time in the United States decreased from 7.4 hours/night to 7.2 hours/night and the percent of adults sleeping less than 6 hours/night increased from 22.3% to 29.2%, though the numbers have been stable since 2004.[9] 69.2% of Americans reported that they did not get enough sleep at least one day in the previous month.[10] Possible explanations for the decreases in sleep duration since the 1980s include new technologies, environment lighting, and long working hours.[11]

Due to decreases in sleep duration over time, many studies on sleep duration focus on short sleep duration or sleep deprivation, while fewer examine long sleep. Long sleep duration is less common (5.0-20.1%) and often occurs concurrently with other comorbidities, such as depression, though the causal relationship is unclear.[12-14]

Measurement of sleep duration (in research settings)

Sleep duration can be measured either subjectively using self-report methods or objectively with actigraphy or polysomnography. Each of the different methods varies in terms of cost, burden, and validity and the choice of measurement can affect a study's results.

Self-report methods of sleep duration range from a single question to sleep diaries to validated questionnaires. Survey questions may include anything from one question

asking about usual sleep time to several questions inquiring about differences in weekday and weekend sleep, sleep quality, and difficulty falling asleep. In a sleep diary/log, participants are asked to record the exact time they turn off the lights for sleep and the time they wake up in the morning. A variety of validated sleep questionnaires exist, including the Pittsburgh Sleep Quality Index (PSQI),[15] among others. Although it is assumed that more questions lead to more valid measures of sleep duration, there is no research comparing the different types of questions in adults. Early epidemiological studies relied on self-reported measures of sleep duration due to ease and cost-effectiveness.

One objective measure of sleep duration is actigraphy. An actigraph is a watch-like device that uses an acceleration sensor to continuously monitor activity with little interference from sleep medicine physicians or study staff. Activity can be measured every one-tenth of a second and several weeks worth of movements can be measured and stored.[16] Software algorithms are then used to download the raw data onto a computer and translate it into usable sleep and wake time information, such as total sleep time, percent of time spent asleep, total wake time, percent of time spent awake, and number of awakenings.[17,18] Many actigraphs employ event markers, which participants use to mark bed and wake times. Actigraphy is often used in combination with sleep logs for verification. To increase reliability and minimize individual differences, actigraphy is best used for at least five days.[19] Because it measures sleep at home for a longer time period, actigraphy can provide information on typical sleep patterns.

Polysomnography is the gold standard for measurement of sleep duration. This procedure, which can occur either in a sleep lab or at home, records multiple physiological measures, including the electroencephalogram (EEG), electrooculogram (EOG), and chin electromyogram (EMG) to determine the stages of sleep. For sleep duration, relevant parameters recorded through polysomnography include lights out, lights on, total recording time, total sleep time, sleep efficiency, sleep latency, and wake after sleep onset (See **Table 1.1** for definitions).[20] Because it requires extensive equipment, polysomnography is more expensive than self-report questionnaires or actigraphy. Another limitation of polysomnography is that it is generally used to assess one night of sleep, so it cannot detect habitual sleep patterns.

Table 1.1: Dictionary of select sleep terms

Total recording time (TRT)	Time from lights out to lights on
Total sleep time (TST)	All REM and NREM sleep during a sleep episode
Sleep efficiency	(TST x 100)/TRT
Sleep latency	Time from lights out to the start of sleep
Wake after sleep onset	Stage W sleep after sleep onset until lights on, formerly duration of wake during the sleep period
NREM Sleep	Non-rapid eye movement sleep
N1 Sleep	Characterized by slow eye movements and decreased muscle activity
N2 Sleep	Makes up half of sleep, characterized by sleep spindles and K complexes
N3 Sleep	Slow-wave sleep, characterized by high-amplitude and low-frequency waves and spindles
REM Sleep	Rapid eye movement sleep, characterized by low amplitude and high-frequency waves
Arousal Index	Number of arousals per hour of sleep

Several studies have compared the validity of the different measurements of sleep duration. Self-reported and objectively measured sleep are moderately correlated (r =

0.43-0.55),[21-23] with mean subjective sleep being almost an hour more. Actigraphy and polysomnography measured sleep duration have been highly correlated (r = 0.89-0.97)[16,18,24,25] though the association is less strong among people who have sleep disorders.[26,27] Compared to polysomnography, actigraphy has high sensitivity but low specificity, as its ability to detect wakefulness is limited in some populations.[17] However, because polysomnography uses many sensors and sometimes occurs away from home, its use may affect sleep. Specifically, the first night a participant is monitored in a sleep study, he or she may experience lower sleep efficiency, less REM sleep, and longer REM latency.[28-30]

In sum, each sleep measurement has inherent strengths and limitations and the determination of the appropriate method depends on the needs and budget of the study as well as participant burden.

Correlates of short sleep duration

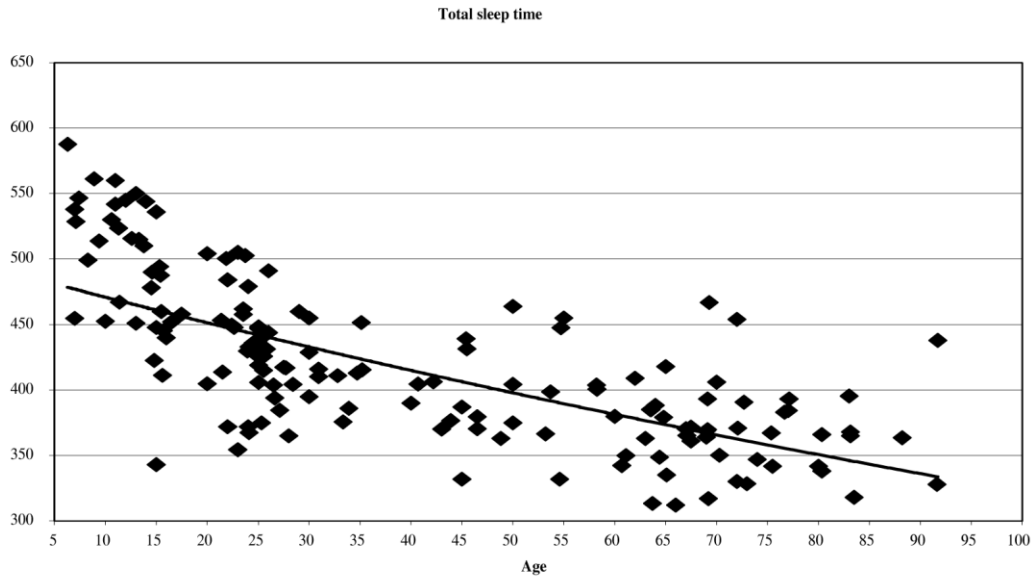
Sex

In most studies, sleep duration was about 0.4-0.8 hours longer for women than men, whether it was measured by self-report, actigraphy, or polysomnography.[13,31-34] The longer sleep duration consistently observed in women may be due to levels of hormones during menstruation, pregnancy, and menopause, or sociological factors such as gender roles.[35]

Age

In most studies, sleep duration declined with increasing age by approximately ten minutes per decade.[31,34,36] Wake after sleep onset (WASO) also increases with age.[31] Relative to younger individuals, older adults tend to have higher N1 and N2 stage sleep, lower N3, lower sleep efficiency, and higher arousal index (see table 1.1 for definitions).[37]

Figure 1.1: Total Sleep Time by Age



(from Ohayon et al 2004)

Race/ethnicity

Previous research has found racial/ethnic differences in sleep duration. In most studies, using both self-report and objective measures of sleep, Whites slept longer than other racial minorities. [32,38,39] Several studies have found that relative to other racial/ethnic groups, a greater percentage of African Americans were more likely to sleep

both shorter (<6 hours) and longer durations (>9 hours), compared to the recommended amount (7-8 hours),[33,40-43] though others found no differences.[34] In the MESA sleep study, White participants slept more than Hispanic and Chinese participants, who slept more than Blacks.[13] Similarly, in NHIS, a greater proportion of Blacks slept less than six hours compared to Mexican Americans, Other Hispanics and Other Non-Hispanics, while Whites had the smallest proportion. [41]

Other

Associations between short sleep duration and measures of socioeconomic status, such as income and education, have not been consistent across studies. Although most studies have found that short sleep is associated with lower education and income,[34,36,42,44] one study found a weak association between more education and income and less sleep.[40] Additionally, individuals who are unmarried have a greater likelihood of short sleep, compared to married individuals.[36,40,45] Single parents also had a shorter sleep duration than adults in two parent families.[46] For alcohol, binge drinking has been associated with short sleep.[36] Both short and long sleep duration have been longitudinally associated with depression.[47]

Introduction to sleep apnea

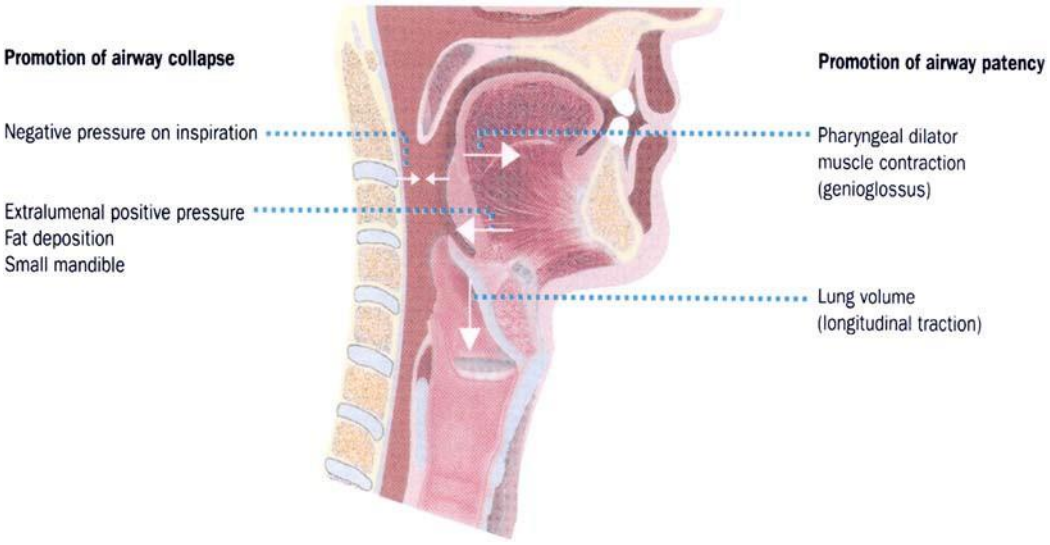
Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing characterized by the repetitive partial or total collapse of the upper airway during sleep. In severe cases, patients suffer from hypoxia (low oxygen in tissues), arousal, and sleep fragmentation, which influence daytime functioning by leading to daytime sleepiness,

reduced cognitive function, and lower quality of life.[48] This contrasts with central sleep apnea, where there is no obstruction and no effort to breathe.[49] Symptoms of OSA include loud snoring and visible pauses in breathing while sleeping, although 85% of people are asymptomatic and unaware that they have the condition.[50]

Pathophysiology

In humans, the upper airway consists of the extrathoracic trachea, pharynx, larynx, and nose, and is used for speech, digestion, and respiration.[51,52] In contrast to other mammals, the upper airway in humans has little support due to a floating hyoid bone, so the pharynx is only supported on its ends. During waking hours, it relies on muscle activity to remain open, but during sleep this activity ceases or is diminished, which results in narrowing or collapsing of the pharynx.[53] Specifically, the airway can collapse for two reasons: intraluminal negative pressure during inspiration and extraluminal pressure resulting from the soft tissue and bony structure surrounding the airway.[54] This collapse results in hypoxia and hypercapnia (high carbon dioxide), which often stimulates arousal from sleep.

Figure 1.2: Pathophysiology of sleep apnea



White 2005

Diagnosis

An OSA diagnosis begins with a sleep history and physical examination, which focuses on signs of obesity, upper airway narrowing, and other OSA risk factors.[55] If the questioning and physical examination indicate the patient is at risk, the patient will undergo full-night polysomnography. In addition to the EEG, EOG, and EMG used in the measurement of sleep duration, the measurement of sleep apnea also requires oronasal airflow, arterial oxygen saturation, respiratory effort, and ECG or heart rate.[20] This procedure identifies obstructive apneas, defined for research as a clear decrease of greater than 50% in airflow at the nose or mouth that occurs for at least ten seconds, and hypopneas, which are a reduction in breathing associated with oxygen desaturation or arousal.[20] The exact reduction in breathing and oxygen desaturation used to define hypopneas varies across studies.

Apneas and hypopneas are then used to calculate the apnea-hypopnea index (AHI), the number of apneas and hypopneas per hour of sleep. AHI cutpoints of 5, 15, and 30 events per hour have been used to indicate mild, moderate, and severe OSA, respectively.[50] A diagnosis of OSA syndrome is given if the AHI exceeds 5 and there are symptoms of daytime sleepiness. Alternatively, the respiratory disturbance index (RDI), defined as the number of apneas, hypopneas, and respiratory effort-related arousals (RERAs) per hour of sleep, is sometimes used.

Although polysomnography is the gold standard, it has several limitations. Polysomnography sometimes requires use of a sleep lab, though it can be done at home. It is also expensive because of the cost of the equipment, and trained staff are needed to interpret the data. Additionally, the sensors can make normal sleep difficult. Due to these limitations, epidemiological studies have often used other definitions of sleep apnea, including self-reported diagnosis, administrative billing codes, and habitual snoring as a surrogate. Survey measures, such as the Berlin Questionnaire, have also been developed to categorize people as being at high or low risk for sleep apnea without the use of polysomnography.[56] However, self-report and administrative data measures only capture those who were actually screened for sleep apnea, and with sleep apnea symptoms strong enough to present for diagnosis, not those with high AHIs but no symptoms. OSA and OSA syndrome are underdiagnosed in the community, with approximately 2-3 times as many people experiencing symptoms than have a diagnosis.[57] Thus, using self-reported diagnosis or administrative data to measure sleep apnea may misclassify individuals whose AHI would meet the criteria for sleep apnea as not having the condition.

Prevalence/Incidence

Because polysomnography is required to diagnose sleep apnea, its prevalence in the population has only been known for approximately twenty-five years. Previously, OSA was only measured among people that presented to sleep clinics because there is no national monitoring system for tracking OSA prevalence. Now, numerous studies in countries across the world have used polysomnography to estimate the prevalence of OSA in the general population.[58-71] In these studies, the prevalence of OSA, defined as an AHI ≥ 5 ranges from 9-37% in men and 4-50% in women, while the prevalence of those with an AHI ≥ 15 was 5-16% in men and in 1-20% women.[72] The prevalence of OSA has differed across these studies due to differences in equipment, definitions, study design, and study populations. Using 2011-2013 data from the Multi-Ethnic Study of Atherosclerosis, which included a community-based sample of men and women aged 54-93, the prevalence of AHI ≥ 15 was 33.8%, the prevalence of AHI ≥ 30 was 15.0% and prevalence of OSA syndrome was 9.8%.[13] Over the past 2 decades, the prevalence of OSA has increased by 14-55%, depending on age, sex, and severity.[65] This may be due in part to the obesity epidemic.

Little data exists on the incidence of OSA, but one study of younger, healthier adults found that 10% of participants with an AHI<5 at baseline had an AHI >15 five years later.[73]

Risk factors

A rich body of literature exists on the risk factors for OSA. However, many studies are outdated and rely on case studies, animal models, or small sample sizes.

Herein we will focus on key, widely-recognized risk factors, which include sex, weight, age, and anatomy, among others.

Sex

Both clinical and epidemiological studies have shown that men have a higher prevalence of OSA than women.[58,60,62-64,68-71,74] though the male-to-female ratio is much higher in clinical populations where all have a diagnosis of sleep apnea, compared to population-based epidemiological studies where fewer study participants have a diagnosis. [75]

A smaller percentage of women present with symptoms such as snoring than men,[75] however, some limited evidence suggests that women may present with different symptoms, including fatigue and lack of energy.[76,77] Women also have a lower AHI than men in NREM but not REM sleep.[78]

There are pathophysiological reasons why there are differences in OSA prevalence between men and women. Men have longer upper airways than women, which may make them more likely to collapse.[79] Limited evidence has also shown that men have more upper airway fat than women,[80] though there has been no difference in other measures such as upper airway collapsibility and pharyngeal muscle activation.[81-83]

Weight

Evidence from a variety of studies and an array of study designs strongly suggest that obesity is causally associated with OSA. A dose-response relationship has been found in many epidemiological studies, where higher BMIs are associated with higher AHI.[58,59,61-64,68,74,84] Longitudinal studies have demonstrated that both high baseline

weight and weight change can speed up the development of more severe OSA.[65,73,85] In randomized trials, weight loss has been associated with decreases in the severity of OSA.[86] Weight loss has also been associated with decreased upper airway collapsibility.[87]

It is currently unclear what measure of obesity is most related to OSA. Neck circumference has been used in prediction models for OSA,[88] likely because it has been more strongly associated with OSA than body mass index.[89] However, there may be sex differences; in one study neck fat was more strongly associated with AHI in women, while abdominal obesity was stronger in men.[90] In another study, OSA had a significant positive association with visceral fat for men, but not women.[91]

Excess body weight may exacerbate OSA through several different pathways. Animal studies suggest that parapharangeal neck fat may directly compress the upper airway.[92] Additionally, abdominal adiposity may lead to displacement of the diaphragm, making the airway more likely to collapse.[93]

Age

The higher prevalence of sleep apnea among older adults has been consistent across studies.[49,59,60,62,94,95] The prevalence increases steadily until around age 60, after which it remains constant. OSA's prevalence is thought to be higher in older adults due to age-related decreases in the negative pressure reflex, increases in parapharyngeal fat pads, lengthening of the soft palate, and changes in the bones around the pharynx.[96] There is some disagreement over whether OSA in older adults is a separate entity as many of its symptoms occur naturally with aging.

Anatomy

Imaging studies have found several anatomic features more common among people with OSA. The most common physical abnormality is a small upper airway, which makes it collapse more easily.[53] The upper airway collapse can be due to skeletal abnormalities, such as short mandible and maxilla length, as well as an inferiorly displaced hyoid bone.[97,98] Soft tissue abnormalities, such as a large tongue or soft palate, may also make the upper airway smaller. Among people with obesity, pharyngeal fat deposits can also narrow and collapse the upper airway. Those who have poor control over upper airway muscles during sleep and a low arousal threshold may also be more likely to develop OSA.[54]

Other

Some studies have found racial differences in OSA, but not all adjusted for important confounders like age and BMI. It has been reported that African Americans have more severe OSA than whites, [99] but results were not consistent across studies, where some found no association[95] or associations only among younger adults.[100] In MESA Sleep, Hispanics and Chinese Americans had a higher mean AHI (16.6 and 16.0, respectively than whites (13.3) and blacks (14.9) before BMI adjustment.[13]

Moderate alcohol consumption has been associated with increases in AHI in both experimental studies that administered alcohol before bedtime[101] and epidemiological studies on habitual alcohol use in men but not women.[102] Alcohol is also associated with longer duration of apnea events,[103,104] though mechanisms are unknown.

Limited evidence exists on the relationship between smoking and OSA, despite many hypothesized pathways.[105] Compared to non-smokers, current, heavy smokers are at greater risk of sleep disordered breathing.[106]

Postmenopausal women have a higher AHI than pre-menopausal women.[107] The prevalence of OSA is lower among women on hormone replacement therapy,[108] though this association is likely due to the healthy user effect and thus not causal.[109]

Hypothyroidism has been associated with higher AHI, although the relationship may be confounded by obesity. [110] [111] Mechanistically, hypothyroidism may make the upper airway more likely to collapse.[111]

Treatment

The gold standard treatment for OSA is continuous positive airway pressure (CPAP), which was first described in 1981.[112] CPAP works by using air pressure to keep the upper airway open during sleep.[113-115] This allows the upper airway to increase in size through positive intraluminal pressure. Normally, optimal pressure is identified through adjustment during an attended polysomnography session at a sleep clinic.[116] CPAP has been used to treat mild, moderate, and severe OSA, but difficulties persist with uptake and compliance. Within the first two weeks of diagnosis and titration, around 25-30% of patients discontinue or fail to begin CPAP treatment.[117] Adequate long-term adherence is often defined as $\geq$ 4 hours on 70% of nights,[118] however only 50-90% of patients on CPAP meet this guideline.[119-122]

Because of CPAP's adherence problems, other methods of PAP treatment have been developed. In contrast to CPAP, which delivers a constant pressure, BPAP (bilevel)

delivers inspiratory and expiratory positive airway pressure separately. Although some patients tolerate BPAP better than CPAP,[123] there is no difference in adherence.[124] APAP (autoadjusting/autotitrating) can automatically select the appropriate level of PAP without an attended titration session. Although some individuals may better tolerate APAP, there is no consistent evidence that adherence is better than CPAP.[125,126]

Oral appliances, including tongue retaining/stabilizing devices and mandibular repositioning devices can also be used to treat OSA, especially for those who did not respond to or are not good candidates for CPAP.[127] For those with severe OSA, oral appliances should only be used after trying CPAP due to their lower efficacy.

Many surgical treatments for OSA exist, including tracheostomy, which can be used as a single solution in patients with life-threatening symptoms who don't respond to other treatments.[128] Although most data is based on case series, tracheostomies have been associated with large decreases in AHI (~80) and oxygen desaturation, and improvements in subjective sleepiness.[129] Other surgical treatments include radiofrequency ablation, palatal implants, uvulopalatal flap (tucks uvula under soft palate), gengioglossus advancement, laser-assisted uvuloplasty (removes small portion of uvula or soft palate), uvulopalatopharyngoplasty, (removes the uvula, residual tonsillar tissue, part of the soft palate, and excess pharyngeal tissue) and maxillomandibular advancement. Radiofrequency ablation, which is often used to reduce snoring, and has been associated with long-term decreases in AHI, though smaller than PAP treatment.[130] Since palatal implants are a relatively new treatment option, limited evidence makes its efficacy and effectiveness unknown.[128] Evidence for the effectiveness of treatments such as laser-

assisted uvuloplasty, uvulopalatopharyngoplasty, and maxillomandibular advancement is based mostly on case series, but suggests that PAP more effectively improves AHI, sleepiness, and quality of life.[128]

Secondary therapies also exist. Because obesity has such a strong effect on OSA, weight loss is a recommended treatment, preferably in combination with PAP or surgery.[131] Bariatric surgery is one option for weight loss, though research on its effects on OSA are limited.[131] Positional therapy, which prevents patients from sleeping in the supine position, is recommended as a secondary therapy, as the upper airway may increase in size in the lateral position. Modafinil can also be used to treat daytime sleepiness, as frequent symptom of OSA, among those with OSA that has no discernable cause.

Sleep duration and cardiovascular disease

Sleep duration has been linked to a variety of cardiovascular outcomes and risk factors, especially obesity. Many of the previous studies of sleep duration and cardiovascular disease (CVD) and/or risk factors have been cross-sectional or used self-reported measures of sleep. For the purpose of this review, we will focus on objectively measured sleep and/or longitudinal studies. In the Coronary Artery Risk Development in Young Adults study (CARDIA), no longitudinal association was found between objective short sleep and BMI, though a cross-sectional association was found.[132] However, CARDIA found that objective short sleep has been longitudinally associated with greater c-IMT in men,[133] higher kidney filtration rates,[134] higher systolic and diastolic blood

pressures and increased risk of incident hypertension,[135] while longer continuously measured objective sleep has been associated with lower incident CAC,[136] and higher total and LDL cholesterol.[137]

Other longitudinal studies, including several meta-analyses, have examined self-reported sleep and cardiovascular risk factors and outcomes. Several systematic reviews and meta-analyses have found prospective associations between short sleep duration and obesity (pooled ORs=1.45 [95%CI 1.25-1.67] and 1.55 [95%CI 1.43-1.68]).[33,138-141] Short sleep duration has been associated with higher levels of C-reactive protein and interleukin-6.[142] A meta-analysis has indicated that both short and long sleep was associated with hypertension, though effects seem to be stronger in younger adults.[143] In a meta-analysis of prospective studies, a U-shaped relationship was found between sleep duration and incident diabetes, with the lowest risk among those who slept 7-8 hours a night.[144] Meta-analyses have also found that self-reported short and long sleep are associated with a variety of cardiovascular outcomes, including coronary heart disease and stroke.[145] For example, the pooled risk ratio for short sleep and coronary heart disease (CHD) was 1.48 (95% CI 1.22-1.80), while for long sleep and CHD it was 1.38 (95%CI 1.15-1.66). Many studies have found associations between both self-reported[146-148] and actigraphic[149-151] short and long sleep and mortality. The vast majority of studies included in these meta-analyses relied on self-report assessment of the exposure.

Pathophysiology of sleep duration and cardiovascular risk factors and disease

There are many hypothesized mechanisms between sleep duration and cardiovascular disease outcomes and risk factors. Much has been written about the

potential pathways through which sleep duration can influence obesity.[152] In experimental studies, short sleep compared to normal street has been associated with increased food intake, including both self-reported and biological changes in hunger and appetite, and increases in ghrelin and decreases in leptin.[139,153] Insufficient sleep may also increase central neuronal responses to high caloric foods, increasing behaviors leading to overeating, as brain imaging data has demonstrated.[154] Short sleepers may also have more opportunities to eat due to the addition of more hours available for eating. In another potential pathway, lack of sleep may lead to fatigue,[155] which can lead to decreased physical activity.

Other potential pathways exist that explain the relationship between sleep duration and CVD. During normal NREM sleep, sympathetic nervous activity decreases and vagal tone increases, which can lead to decreases in metabolic rate, blood pressure, and heart rate.[156,157] Experimental studies have found that acute sleep deprivation is associated with increases in blood pressure,[158,159] heart rate,[160] c-reactive protein,[161] norepinephrine,[160] pulse wave velocity,[162] cardiac output, [162] and endothelial dysfunction, although findings have not been consistent across studies. Short sleep in laboratory studies has also been associated with decreases in muscle sympathetic nervous activity and glucose tolerance.[163] Sleep deprivation has also been shown to attenuate nocturnal blood pressure dipping and increase morning surge,[164] both of which have been associated with CVD.[165] Additionally, a crossover study has shown that sleep deprivation can affect left ventricular diastolic function and QT intervals.[166]

Long sleep had no significant impact on any outcome in experimental studies, indicating that the relationship between long sleep and CVD may not be causal.[11] Long sleep may be a consequence of disease or part of the dying process, and associations in observational studies may be due to residual confounding. It may also reflect measurement error due to a reliance on self-reported measures of sleep duration.

OSA and Cardiovascular Disease

OSA has been linked to a variety of CVD risk factors and outcomes. Many of the early population-based studies were cross-sectional and used self-reported or administrative data to measure sleep apnea, but more longitudinal studies using polysomnography have been published in recent years. These include both studies on the associations between sleep apnea and cardiovascular risk factors/disease and studies on CPAP treatment and cardiovascular risk factors/disease, including some trials of randomized CPAP treatment. Challenging interpretation, categorization of the sleep apnea exposure often differs across studies.

Meta-analyses have shown that those with OSA have higher levels of total cholesterol,[167] triglycerides and LDL and lower HDL,[168] while RCTs of CPAP treatment have been associated with lower total cholesterol, but no change in triglycerides, LDL, and HDL.[169] Longitudinal studies have shown that OSA is associated with an increased risk of diabetes,[170] though CPAP trials to improve glycemic control among OSA patients with diabetes have been mixed.[171,172] Additionally, randomized controlled trials have demonstrated lower rates of incident hypertension among CPAP users.[167,173] Associations

have also been found between OSA measured via polysomnography and risk of coronary heart disease,[174] stroke,[175] heart failure,[174] and mortality,[176-178] while only self-reported OSA has been linked to atrial fibrillation. [179]

Although studies randomizing OSA patients to CPAP have been conducted for hypertension, few studies have examined the effect of CPAP on cardiovascular events due to difficulties with CPAP adherence and sample size.[167,180] In the SAVE trial, there was no association between CPAP use compared to usual care and incident CVD events, though adherence to CPAP was poor.[180]

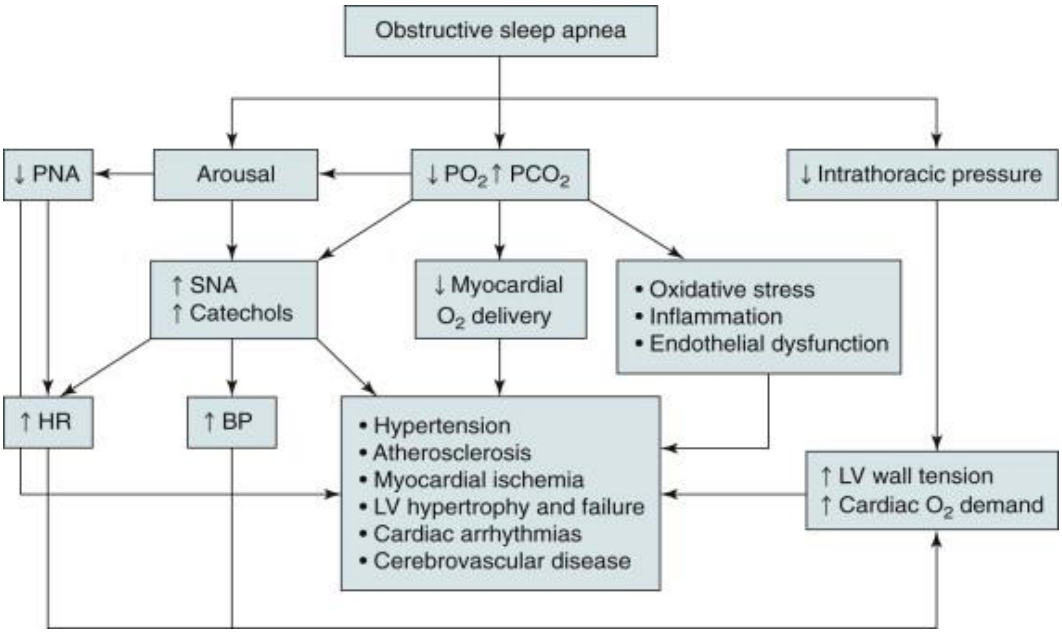
In general, studies on OSA and CVD show a dose-response relationship, where associations with CVD were stronger among those with severe OSA and weaker among those with mild OSA.[181] Meta-analyses have also indicated that these associations are stronger in men than women.[182] Furthermore, better adherence to CPAP has been associated with lower risk of CVD mortality.[183]

Pathophysiology of sleep apnea and cardiovascular risk factors and disease

There are several potential pathways that may explain the relationship between OSA and CVD though many are interrelated. In general, OSA alters the normal cardiometabolic functions that occur during NREM sleep. The hypercapnia and hypoxemia that occur during an apneic event cause an increase in sympathetic nervous system activity,[184] which persists during waking hours.[185] Additionally, those with OSA have more blood pressure variability but less heart rate variability,[186] which is linked to CVD and its risk factors. Hypoxia can also release endothelin,[187,188] which may raise blood pressure in people with OSA.[189] Sleep apnea has also been associated with higher

levels of a variety of different inflammatory markers, including plasma cytokines, C-reactive protein, leukocyte activation,[190] among others, which have also been associated with CVD risk. Because of sleep apnea's frequent hypoxia and re-oxygenation, an effect on oxidative stress has been hypothesized, though several CPAP trials have found no relationship.[191-193] A similar relationship is hypothesized between sleep apnea and endothelial dysfunction, possibly operating through increased sympathetic nervous system activity, inflammation, oxidative stress, and reductions in the bioavailability of endothelial nitric oxide. [194] **Figure 1.3**, taken from the "Fundamentals of Sleep Medicine" text, illustrates hypothesized pathways between OSA and CVD.

Figure 1.3: Pathways between OSA and CVD



Chapter 2: Manuscript 1 - Sleep indices and eating behaviors in young adults: Findings from Project EAT

Abstract

Objective: To test the associations between sleep indices and eating behaviors in young adults, a group vulnerable to suboptimal sleep.

Design: Cross-sectional analysis of survey measures of sleep (i.e., time in bed, variability, timing, and quality) and dietary patterns (i.e., breakfast skipping, eating at fast-food restaurants, sports and energy drinks, sugar-free, sugar-sweetened, and caffeinated beverages).

Setting: Minneapolis/St. Paul metropolitan area of Minnesota (USA)

Subjects: A total of 1854 respondents (20-30 years, 55.6% female) to the 2008-2009 survey conducted for the third wave of the population-based Project EAT (Eating and Activity in Teens and Young Adults) study.

Results: After adjustment for demographic and behavioral covariates in linear regression models, those who went to bed after 12:30 AM consumed 0.3 more servings per day of sugar-sweetened beverages, consumed 1.7 times more energy drinks, skipped breakfast 1.8 more times per week, and consumed fast food 0.3 more times per week compared to

those who went to bed before 10:30 PM. Reported sleep quality in the lowest versus highest quartile was associated in adjusted logistic regression models with more intake of energy drinks, (Q4 vs Q1 Prevalence Ratio: 1.86, 95% CI: 1.29-2.42) sports drinks, (Q4 vs Q1 PR: 1.28, 95% CI: 1.00-1.55) and breakfast skipping. Time in bed and sleep variability were associated with only a few eating behaviors.

Conclusions: Some, but not all, sleep indices were related to problematic eating behaviors. Sleep habits may be an important behavior to address in interventions and policies that target improvements in eating patterns and health outcomes.

Background

Currently, the American Academy of Sleep Medicine and the Sleep Research Society recommend that adults should sleep at least seven hours per night.[195] Failing to meet this recommendation has been associated with poor physical health,[145] mental health,[47] and quality of life.[196-198] National survey data indicate that young adults, aged 25-34, are particularly likely to get insufficient sleep; in 2014, 28% reported sleeping fewer than 7 hours per night.[8] Although short sleep duration and its relation to dietary intake has been examined in adolescents,[199,200] there is scant research on this relationship in young adults, who are undergoing major life transitions and engaging in independent decision-making for the first time.

Most research among adults has involved short-term experiments conducted in sleep labs,[201] which do not provide information on habitual behaviors among free-living adults. The few observational studies of adults have examined how sleep duration may be related to obesity and energy intake with inconsistent results, [139,202] but the specific aspects and patterns of dietary intake correlated with short sleep duration have scarcely been explored.[203,204] Even less is known about the association of sleep quality, variability, and timing with dietary factors.[205] Furthermore, most prior studies were conducted in predominantly white populations, despite previous research exposing racial/ethnic[33,40,42] and socioeconomic differences in sleep duration.[206,207] A recent American Heart Association scientific statement named the inclusion of more diverse populations a top sleep research priority.[208]

The Project EAT (Eating and Activity in Teens and Young Adults) study provides an opportunity to investigate the potentially bidirectional relationship between several sleep indices and dietary factors in a racially, ethnically and socioeconomically diverse population of young adults. We hypothesized that young adults who reported inadequate versus recommended amounts of sleep would consume more caffeinated and sugar-sweetened beverages and report more frequent breakfast skipping and eating at fast-food restaurants.

Methods

Project EAT was designed to study dietary intake, physical activity, and weight among young people. Baseline data were collected in 1998-1999, when 4,746 middle and high schools students aged 11-18 years from 31 socioeconomically and racially/ethnically diverse schools in the Minneapolis/St. Paul metropolitan area of Minnesota completed questionnaires and anthropometric measures.[209] A 10-year follow-up survey (EAT-III) was completed in 2008-2009 by mailing all original participants an invitation to complete questionnaires on paper or online. A total of 2,287 young adults completed this third wave of data collection, representing 66.4% of those who could be contacted.[210] At the time of EAT-III, participants were 20-30 years old. For the present analysis, we limited the sample to participants whose third wave survey data included plausible reports of dietary intake and sleep (n = 1,854). The University of Minnesota IRB approved all study protocols, and participants provided informed consent.

The original Project EAT survey was modified for EAT-III to improve the relevance of items for young adults and to investigate new research areas. Focus groups

tested an initial draft and feedback was used to alter problematic survey measures and to expand on areas of importance. A revised survey was tested in a different sample to examine test-retest reliability over one to three weeks. Additional details of the survey development process have been described elsewhere.[211]

Sleep variables

Participants were asked about their usual bedtime and wake time on both weekdays and weekends, which were used to calculate average weekday and weekend *time in bed*.[212] These items were drawn from a questionnaire previously used in studies of adolescent sleep,[213,214] and similar questions have been significantly correlated with both sleep diaries and actigraphy. [215] Average daily time in bed was calculated using the following formula: weekday time in bed*5/7 + weekend time in bed*2/7, and was modeled categorically (<7 hours, 7-8 hours, 8-9 hours, and >9 hours).

We also examined *sleep variability* by calculating the absolute value of the difference between weekday and weekend time in bed, which was modeled in quartiles (<0.5 hours, 0.5-<1 hour, 1-1.5 hours, >1.5 hours). *Sleep timing* was measured by averaging weekend and weekday bedtimes and modeling them in four categories (before 10:30 PM, 10:30-11:30 PM, 11:30 PM-12:30 AM, after 12:30 AM). *Sleep quality* was measured using the following question on the Kandel and Davies depressive symptoms questionnaire:[216] "During the past 12 months, how often have you been bothered or troubled by having trouble going to sleep or staying asleep?" (test-retest r = 0.64). Possible responses to this question include not at all, sometimes, or very much.

Dietary variables

Questions on frequency of skipping *breakfast* and eating at a *fast-food* restaurant were assessed on the Project EAT-III survey. Breakfast was assessed with the following question: "During the past week, how many days did you eat breakfast?" with five possible responses ranging from never to every day (test-retest r = 0.82). Fast food was assessed with the following question: "In the past week, how often did you eat something from a fast food restaurant (like McDonald's, Burger King, Hardee's etc.)?" (test-retest r = 0.48). Six possible responses were given, ranging from never to more than 7 times. Both variables were treated as continuous.

Questions on *energy* and *sports drink* consumption were also assessed on the Project EAT-III survey. Energy drink consumption was assessed with the following question: "In the past year, how many times did you usually drink an energy drink (such as Red Bull, Full Throttle, Rockstar, etc.)?" Sports drink consumption was assessed with the following question: "In the past year how many times did you usually drink a sports drink (such as Gatorade, PowerAde, etc.)?" Seven possible responses were given, ranging from less than once per month to 2 or more per day. Based on the distribution of the variables,[217] energy and sports drinks were dichotomized into two categories: at least one drink per week and less than one drink per week (test-retest agreement = 94% for sports drinks, 97% for energy drinks).

Information on beverages including *sugar-sweetened beverages* (SSBs), *sugar-free beverages*, and *caffeinated beverages*, was taken from a semi-quantitative food-frequency questionnaire (FFQ) that was administered at the same time as the Project

EAT-III survey. This FFQ measured multi-vitamins, dietary supplements, and intake of 151 foods. The reproducibility and validity compared to diet records for measuring beverages has been assessed, and moderate correlations have been found (mean r for reproducibility = 0.59, mean validity r = 0.63).[218] Sugar-sweetened, sugar free, and caffeinated beverages were assessed with 9 response categories, ranging from never or less than once a month to 6+ per day. This was translated into daily servings with a single serving defined as one glass, bottle, or can. The sugar-sweetened beverages variable was created by summing the responses to questions on carbonated beverages with caffeine and sugar (e.g., Coke, Pepsi, Mountain Dew, Dr. Pepper), other carbonated beverages with sugar (e.g., 7-Up, Root Beer, Ginger Ale, Caffeine-Free Coke), and other sugared beverages (punch, lemonade, sports drinks, or sugared ice tea). The sugar-free beverages variable was created by summing responses to questions on low-calorie beverages with caffeine (e.g., Diet Coke, Diet Mountain Dew) and other low-calorie beverages without caffeine (e.g., Diet 7-Up). The caffeinated beverages variable was created by summing the responses to the questions on low-calorie beverages with caffeine and carbonated beverages with caffeine and sugar along with additional items that assessed intake of tea with caffeine including green tea (8 oz), coffee with caffeine (8 oz), and dairy coffee drink (e.g. cappuccino, 16 oz). These variables were treated as continuous.

Covariates

Demographic characteristics including sex, ethnicity/race, age, education, and marital status were self-reported. Depressive symptoms were assessed via a six-item scale validated for use in young people.[216] Items on this questionnaire related to sleep were not

included as covariates, and the remaining items on sadness, hopelessness, nervousness, and worry were summed and categorized into three groups. Physical activity was assessed with the 3-item Godin Leisure-time Exercise questionnaire, which calculates a weekly leisure activity score.[219] Alcohol was measured in grams. These variables were included as covariates due to their bidirectional relationships with sleep. [220,221]

Analysis

Descriptive statistics were calculated to examine sociodemographic and behavioral characteristics by time in bed category. Based on the outcome, either linear or logistic regression was used to model the cross-sectional relationship between each sleep exposure and each dietary outcome. Adjusted probabilities standardized to the total population were calculated for each sleep category in the logistic models, and these probabilities were used to calculate prevalence ratios for each outcome. Model 1 adjusted for age, sex, race/ethnicity, education, marital status, while Model 2 added depressive symptoms and physical activity. For models with sleep variability, timing, and quality as the exposure, model 3 added time in bed. We also examined effect modification by gender, as previous research has found different relationships between sleep habits and dietary intake for men and women.[222] A sensitivity analysis with an additional time in bed category of less than six hours per night was also performed. All analyses used inverse probability weighting to account for differential loss to follow up.[223]

Results

The mean age in the analytic sample was 25.4 years (SD=1.6), and 55.6% were female. Participants self-reported sleeping a mean of 8.3 (SD=1.2) hours per night. The

distribution of sleep times was: 11.5% slept fewer than 7 hours per night, 26.6% slept 7-8 hours, 36.2% slept 8-9 hours, and 25.8% slept more than 9 hours. In regards to daily dietary intake, on average, participants consumed 0.9 servings of sugar-sweetened beverages, 0.7 servings of caffeinated beverages, and 0.4 servings of sugar-free beverages. Per week, participants consumed breakfast an average of 3.9 times and ate something from a fast food restaurant on 1.6 occasions. The proportion of the sample that reported consuming at least one energy drink per week was 18.0%, and consuming at least one sports drink per week was reported by 30.2%.

Table 2.1 shows sociodemographic and behavioral characteristics by time in bed category. Those who slept fewer than 7 hours per night were more likely to be male, non-white, have less formal education, and have a higher mean depressive symptoms score relative to those who slept longer. Those with later bedtimes were more likely to be male, have less formal education, and report higher mean depressive symptoms. Good sleep quality was more common among men and those with more education (data not shown).

Table 2.2 shows the mean intake of beverages and mean frequency of skipping breakfast and eating at a fast-food restaurant by categories of sleep variables (time in bed, variability, timing, and quality). After adjustment for demographics, some associations were found between sleep indices and eating behaviors, particularly for sleep timing, though many associations were not significant. Those who went to bed after 12:30 AM consumed 0.3 more servings per day of sugar-sweetened beverages, skipped breakfast 1.8 more times per week, and consumed fast food 0.3 more times per week compared to those who went to bed before 10:30 PM. No strong associations were found between

sleep timing and caffeinated or sugar-free beverages. Results were similar after adjustment for depressive symptoms, physical activity, alcohol, and time in bed.

For the remaining sleep indices, there were few strong statistically significant associations with the continuous eating behaviors after adjustment for demographics. Compared to those who slept 7-8 hours per night, those who slept < 7 hours consumed an average of approximately 0.2 more servings per day of caffeinated beverages [0.87 (95%CI 0.71-1.04) servings vs 0.66 (95%CI 0.57-0.75) servings] ($p = 0.03$). Compared to those with low sleep variability, those in the highest sleep variability quartile consumed fast food 0.25 more times per week ($p = 0.02$). As an indicator of sleep quality, those reporting 'very much' difficulty falling/staying asleep skipped breakfast approximately one additional time every ten days compared to those who reported no trouble falling/staying asleep ($p < 0.001$).

Effect modification by sex was also examined and stratified analyses for significant multiplicative interaction terms can be found in **Table 2.3**. Although the frequency with which men skipped breakfast was unrelated to time in bed, women who slept <7 hours per night skipped breakfast nearly one additional time per week compared to women who slept 7-8 hours (p for interaction < 0.01). Men who went to bed after 12:30 AM consumed 0.5 more caffeinated beverages and 0.25 more sugar-free beverages than men who went to bed before 10:30 PM, while women consumed approximately the same amount of those beverages regardless of bedtime (p for interaction < 0.01).

Table 2.4 shows prevalence ratios (PR) for intake of energy and sports drinks (modeled dichotomously: ≥1 drink per week and <1 drink per week) by sleep exposure

category. After adjustment for demographics, those who slept fewer hours, had more sleep variability, reported later bedtimes, and reported 'very much' difficulty falling/staying asleep were more likely to consume energy drinks, although the associations were not statistically significant across all models. For sleep timing, those who reported going to bed after 12:30 AM were 1.83 (95% CI 1.10-2.55) times more likely to consume at least one energy drink per week than those who went to bed at 10:30 PM or earlier. Those who reported >8 hours of sleep were less likely to consume sports drinks than those who slept 7-8 hours per night, while those who reported 'very much' difficulty falling/staying asleep were more likely to consume sports drinks that those who reported no difficulty [PR =1.24 (95% CI 0.99-1.49)].

Sensitivity analyses were also performed for all outcomes with an additional time in bed category: < 6 hours (**Supplemental Table 2.1**). Although precision was poor, those who slept < 6 hours drank approximately 0.35 more daily servings of caffeinated drinks, 0.45 more daily servings of sugar-sweetened beverages, and skipped breakfast one additional time every ten days compared to those who slept 7-8 hours. Those who slept fewer than 6 hours were also more likely to consume energy drinks (PR=1.55 [0.59, 2.50]). No statistically significant associations were found for sugar-free beverages, fast food, or sports drinks.

Discussion

In this population-based study of young adults, we provide new evidence that sleep characteristics beyond time in bed are associated with selected eating behaviors. Late sleep timing was most consistently associated with poor eating behaviors, including

consumption of energy drinks, sugar-sweetened beverages, fast food, and breakfast skipping. Fewer associations were found for other sleep indices.

In this study, going to sleep late was directly associated with four of the seven poor eating behaviors, including more frequent consumption of energy drinks and sugar-sweetened beverages, and frequency of eating at fast food restaurants, as well as breakfast skipping. These findings are consistent with another small cross-sectional study, where actigraphy-measured late sleep timing was associated with more servings of full-calorie soda and fast food per week, though results were not adjusted for confounders.[205] Previous research also found that delaying bedtimes was not associated with more caffeine use, [224] while we found a small association between sleep timing and caffeinated beverages that was no longer significant after adjustments for depressive symptoms, alcohol, and physical activity. Research on other dietary measures has found actigraphy-measured sleep timing was not associated with the Alternative Healthy Eating Index-2010 or any of its components.[225]

Less time in bed, an approximation of sleep duration, was associated with more caffeinated beverage consumption, while more time in bed was associated with less sports drink consumption. The relationship between sleep duration (or time in bed) and eating behaviors has been examined more frequently in previous literature than the relationships between other sleep indices and eating behaviors. Observational studies on time in bed or sleep duration and caffeinated beverages have similarly found inverse associations,[203,224,226,227] although one found no association.[227] Additionally, those who slept fewer than six hours a night were more likely to skip breakfast[203] and consume

sugar-sweetened beverages, including caffeinated beverages, than those who slept 7-8 hours a night.[228] In the current study, the proportion sleeping at least 7 hours per night was 88.5%, which contrasts with national survey data where only 67.8% of 18-24 year olds and 62.1% of 25-34 year olds reported sleeping at least seven hours per night, though the self-report methods of these two studies were different.[8] Because of the narrow distribution of sleep in our sample, we did not have sufficient precision to consider more extreme categories of shorter sleep duration as the primary exposure, though in sensitivity analyses we showed that those who slept fewer than six hours a night skipped more breakfast and consumed more SSBs than those sleeping 7-8 hours per night. Studies of adults and adolescents have reported that those with short sleep duration ate fast food more often than those meeting sleep recommendations,[204,229] a finding not replicated in our study.

In this study, poor sleep quality was significantly associated with six of the seven poor eating behaviors, but associations only remained for energy drinks, sports drinks, and skipping breakfast after adjustment for depressive symptoms, alcohol, and physical activity. Previous research on sleep quality and intake of caffeine/energy drinks has been mixed, with studies finding null[226,230] or inverse associations.[231-234] However, a study of Japanese female workers found that poor sleep quality was associated with greater sugar-sweetened beverage consumption and breakfast skipping.[235] Studies involving other dietary and eating measures have found associations between poor sleep quality and low intake of vegetables and fish[235] as well as lower adherence to the Mediterranean diet.

Sleep variability has been rarely measured in population-based studies, especially in relation to diet. In the present study high sleep variability was associated with greater fast food and energy drink consumption. Previous studies have found positive associations between sleep variability and obesity, [236,237] including a mediating influence of diet variables,[238] though no association with obesity was found in a previous Project EAT analysis.[212]

Overall, in this study, associations between sleep and eating behaviors were not consistent across indices. This may reflect measurement error, as described below, or may indicate unique dimensions of sleep. While some aspects of sleep, like duration, can be measured objectively, self-reported sleep quality is inherently subjective, and thus may capture a different aspect of the sleep process or reflect differences in self-reporting. In this study, the four sleep indices used were weakly correlated (r's <0.2). Future research should continue to focus on multiple dimensions to obtain a complete picture of sleep. Prospective data are also needed to further elucidate the relationship between sleep and dietary intake.

We observed effect modification by sex for some exposure-outcome combinations. Previous laboratory research also found differences, where men consumed more daily calories than women after sleep restriction.[222] Differences could be due to gender biology (e.g. levels of hormones), differences in social desirability that impact self-reporting, or ways that society influences coping during sleep restriction periods differentially by gender.[35] In general, sleep duration is longer in women than men.[13,32]

The relationship between sleep and diet is likely complex, and potentially bidirectional. Caffeinated drinks, such as soda and energy drinks, block adenosine receptors, which prevent the sleep promoting effects of adenosine, and thus reduce sleep duration. However, people who are sleep deprived may consume more caffeinated drinks to feel more alert.[239] Short sleep duration may also influence diet by providing more time and opportunities for eating, allowing people to be more sensitive to food rewards, decreasing restraint, and changing concentrations of hormones that influence appetite, such as leptin and ghrelin.[240] However, limited evidence also suggests that nutrients that help synthesize serotonin may also promote sleep.[241]

Other sleep indices likely act through similar pathways. Although the mechanisms for associations between sleep timing and diet are not fully elucidated, possible mechanisms include circadian disruption and greater exposure to light at night.[242,243] People with high sleep variability may also have irregular eating patterns due to variation in their sleep-wake pattern, which may contribute to irregularity in the synchronization of eating and sleep timing.[236]

This study has several limitations, including measurement error in the sleep and dietary variables, which were both assessed via survey. Self-reported and objectively measured sleep are moderately correlated,[21-23] but the degree of correlation varies by important confounders such as obesity and depression. Dietary intake was self-reported and likely represents an underestimation of intake. Previous research has found moderate to high reproducibility and validity of FFQs compared to diet records, though both measures are self-reported.[218] Combined, these errors in measurement may have biased

the estimates towards (likely) or away from the null (less likely). Additionally, this cross-sectional study inherently offers no information on temporality and the causal pathway between sleep and diet is at times unclear, particularly for caffeine and energy drinks. These associations between sleep and diet may also be due to a shared cause. We also performed many statistical tests, so it is possible that some of the results may be due to chance.

Despite these limitations, this study has several strengths. Quality observational studies on sleep duration and dietary intake are limited, due to an emphasis on short-term experiments conducted in sleep labs, which do not provide information on habitual behaviors among free-living adults. Another strength of this study is the diverse and population-based sample of young adults. Use of this sample aligns with the 2016 American Heart Association Scientific Statement that highlighted the need for sleep studies to include diverse populations.[208] Additionally, the measurement instruments used in this study employed multiple indices of sleep and diet, which allowed the capture of these behaviors in several different dimensions.

Sleep and diet are both inherently vital health behaviors. Short sleep duration is highly prevalent, especially among young adults.[8] Dietary quality may be improving,[244] but the vast majority of the US population is still not meeting dietary recommendations. Though this study found some cross-sectional associations between sleep and eating behaviors, particularly as related to sleep timing, many associations were not significant, and further longitudinal and randomized studies with objective measures of sleep are needed to clarify the directionality of the sleep-diet relationship. Young adults often

experience significant changes in their establishment of an independent life, including attainment of higher education, new employment, getting married, and having children. As such, if the relationships found between sleep and eating behaviors in this study are causal, sleep-friendly interventions and policies may have the potential, along with other risk factors, to reduce obesity in this population. Identifying effective obesity prevention measures for young adults is particularly important, as at this age range there is the potential to set long-term health habits.

Table 2.1: Participant characteristics by sleep duration category: Project EAT

	<7 hours	7-8 hours	8-9 hours	≥ 9 hours
N (%)	203 (11.5)	471 (26.6)	642 (36.2)	457 (25.8)
Demographics				
Age, mean years ± SD	25.5 ± 1.7	25.6 ± 1.5	25.3 ± 1.5	25.1 ± 1.8
% Female, n (%)	87 (42.8)	240 (51.0)	366 (57.0)	292 (64.0)
Race/Ethnicity, n (%)*				
White	93 (9.8)	255 (27.0)	384 (40.6)	214 (22.6)
Asian	39 (12.1)	90 (28.5)	92 (29.1)	95 (30.1)
Black	44 (16.1)	64 (23.1)	82 (29.6)	86 (31.1)
Hispanic	9 (10.0)	27 (30.2)	37 (40.8)	17 (19.1)
Mixed/Other	15 (12.1)	31 (23.9)	43 (33.4)	39 (30.6)
Education, n (%) *				
Less than high school	11 (16.2)	8 (11.2)	18 (25.7)	32 (46.9)
High school/GED	86 (12.8)	178 (26.6)	216 (32.2)	191 (28.4)
Vocational or associates degree	60 (13.4)	115 (25.6)	153 (33.9)	122 (27.1)
College graduate	45 (7.8)	169 (29.0)	255 (43.9)	112 (19.2)
Married, n (%)	38 (18.6)	131 (28.1)	166 (25.9)	83 (18.1)
Behavioral Characteristics, Mean ± SD				
Physical activity, hrs MVPA/wk	4.4 ± 4.4	4.1 ± 3.7	4.3 ± 3.7	3.5 ± 3.8
Depression Scale	19.2 ± 5.0	17.9 ± 4.9	18.0 ± 4.6	19.0 ± 4.8
Outcomes, mean servings ± SD				
§Caffeinated drinks per day	0.9 ± 1.3	0.7 ± 1.0	0.7 ± 1.0	0.7 ± 1.2
¶Sugar-sweetened beverages per day	1.1 ± 1.4	0.8 ± 1.2	0.8 ± 1.1	0.9 ± 1.5
□Sugar-free beverages per day	0.4 ± 1.1	0.4 ± 0.8	0.4 ± 0.7	0.3 ± 0.8
Breakfast consumption per week	3.6 ± 2.4	3.9 ± 2.3	4.2 ± 2.3	3.6 ± 2.5
Fast food consumption per week	1.7 ± 1.8	1.5 ± 1.6	1.5 ± 1.6	1.7 ± 1.6
†Energy drinks, n (%)	70 (26.8)	58 (13.1)	93 (17.0)	98 (18.7)
†Sports drinks, n (%)	101 (38.6)	125 (28.3)	167 (30.5)	143 (27.3)

*Row percentages
MVPA: moderate-vigorous physical activity, SD: standard deviation
§Caffeinated beverages were defined as low-calorie beverages with caffeine (e.g. Diet Coke, Diet Mountain Dew), carbonated beverages with caffeine and sugar (e.g., Coke, Pepsi, Mountain Dew, Dr. Pepper), tea with caffeine including green tea, coffee with caffeine, and dairy coffee drink (e.g. cappuccino)
¶Sugar-sweetened beverages were defined as carbonated beverages with caffeine and sugar, other carbonated beverages with sugar (e.g. 7-Up, Root Beer, Ginger Ale, Caffeine-Free Coke), and other sugared beverages (punch, lemonade, sports drinks, or sugared ice tea)
□Sugar-free beverages were defined as low-calorie beverages with caffeine and other low-calorie beverages without caffeine (e.g. Diet 7-Up)

[†]Energy and sports drink consumption defined as ≥ one drink per week compared to < one drink per week

Table 2.2: Adjusted mean dietary intake (95% confidence interval) by categories of sleep duration, variability, timing, and quality: Project EAT

Time in Bed	<7 hours	7-8 hours	8-9 hours	>9 hours
N	203	471	642	457
		(Referent)		
Caffeinated drinks per day				
Model 1	0.87*	0.66	0.68	0.74
	(0.71, 1.04)	(0.57, 0.75)	(0.60, 0.77)	(0.63, 0.85)
Model 2	0.87*	0.67	0.70	0.71
	(0.71, 1.04)	(0.58, 0.76)	(0.61, 0.78)	(0.61, 0.82)
Sugar-sweetened beverages				
Model 1	0.99	0.85	0.83	0.94
	(0.79, 1.18)	(0.74, 0.97)	(0.73, 0.93)	(0.79, 1.09)
Model 2	0.99	0.86	0.85	0.91
	(0.80, 1.17)	(0.74, 0.98)	(0.75, 0.95)	(0.76, 1.05)
Sugar-free beverages				
Model 1	0.47	0.36	0.33	0.33
	(0.33, 0.62)	(0.29, 0.43)	(0.28, 0.39)	(0.26, 0.40)
Model 2	0.47	0.36	0.34	0.32
	(0.32, 0.61)	(0.29, 0.43)	(0.28, 0.40)	(0.25, 0.39)
Breakfast consumption per week				
Model 1	3.78	3.94	4.07	3.66
	(3.41, 4.14)	(3.72, 4.15)	(3.87, 4.27)	(3.39, 3.92)
Model 2	3.77	3.92	4.04	3.69
	(3.42, 4.12)	(3.70, 4.14)	(3.84, 4.24)	(3.43, 3.95)
Fast food consumption				
Model 1	1.56	1.53	1.58	1.72
	(1.27, 1.85)	(1.38, 1.69)	(1.44, 1.71)	(1.56, 1.89)
Model 2	1.56	1.55	1.60	1.71
	(1.27, 1.85)	(1.39, 1.70)	(1.47, 1.73)	(1.54, 1.88)
Sleep variability	< 0.5 hours	0.5 - <1 hour	1 – 1.5 hours	> 1.5 hours
N	339	364	571	500
	(Referent)			

Caffeinated drinks				
Model 1	0.71	0.72	0.67	0.76
	(0.59, 0.84)	(0.60, 0.83)	(0.59, 0.75)	(0.66, 0.86)
Model 2	0.72	0.71	0.68	0.75
	(0.60, 0.84)	(0.60, 0.83)	(0.60, 0.77)	(0.66, 0.84)
Model 3	0.72	0.71	0.69	0.75
	(0.59, 0.84)	(0.60, 0.83)	(0.60, 0.77)	(0.65, 0.84)
Sugar-sweetened beverages				
Model 1	0.95	0.86	0.86	0.88
	(0.79, 1.10)	(0.73, 1.00)	(0.74, 0.98)	(0.76, 0.99)
Model 2	0.95	0.86	0.88	0.86
	(0.80, 1.10)	(0.73, 0.99)	(0.76, 1.00)	(0.75, 0.97)
Model 3	0.95	0.86	0.88	0.86
	(0.79, 1.10)	(0.73, 0.99)	(0.76, 1.00)	(0.75, 0.97)
Sugar-free drinks				
Model 1	0.29	0.38	0.34	0.39*
	(0.22, 0.36)	(0.29, 0.47)	(0.28, 0.40)	(0.32, 0.47)
Model 2	0.30	0.38	0.35	0.39
	(0.22, 0.37)	(0.29, 0.47)	(0.28, 0.41)	(0.32, 0.46)
Model 3	0.30	0.38	0.35	0.39
	(0.23, 0.38)	(0.29, 0.47)	(0.28, 0.41)	(0.31, 0.46)
Breakfast consumption				
Model 1	3.81	4.10	3.95	3.74
	(3.52, 4.10)	(3.85, 4.33)	(3.73, 4.17)	(3.51, 3.97)
Model 2	3.77	4.09	3.93	3.77
	(3.49, 4.06)	(3.85, 4.33)	(3.71, 4.15)	(3.54, 4.00)
Model 3	3.81	4.07	3.94	3.75
	(3.52, 4.10)	(3.83, 4.31)	(3.72, 4.16)	(3.52, 3.98)
Fast food consumption				
Model 1	1.47	1.60	1.53	1.77*
	(1.30, 1.64)	(1.41, 1.79)	(1.40, 1.67)	(1.60, 1.93)
Model 2	1.49	1.61	1.55	1.76*
	(1.31, 1.66)	(1.42, 1.79)	(1.41, 1.68)	(1.59, 1.93)
Model 3	1.45	1.62	1.55	1.77*
	(1.28, 1.63)	(1.43, 1.80)	(1.41, 1.68)	(1.60, 1.94)
Sleep Timing	≤ 10:30 PM	10:30-11:30 PM	11:30 PM-	> 12:30 AM

			12:30 AM	
N	327 (Referent)	497	390	560
Caffeinated drinks				
Model 1	0.64	0.66	0.72	0.80*
	(0.53, 0.75)	(0.57, 0.75)	(0.61, 0.82)	(0.71, 0.90)
Model 2	0.66	0.67	0.71	0.79
	(0.55, 0.77)	(0.57, 0.76)	(0.61, 0.82)	(0.69, 0.88)
Model 3	0.67	0.68	0.71	0.77
	(0.56, 0.78)	(0.58, 0.77)	(0.61, 0.82)	(0.68, 0.87)
Sugar-sweetened beverages				
Model 1	0.73	0.78	0.88	1.05**
	(0.60, 0.87)	(0.68, 0.87)	(0.75, 1.02)	(0.93, 1.18)
Model 2	0.75	0.79	0.88	1.04**
	(0.61, 0.88)	(0.69, 0.90)	(0.75, 1.01)	(0.92, 1.16)
Model 3	0.75	0.80	0.88	1.04**
	(0.61, 0.88)	(0.69, 0.90)	(0.75, 1.02)	(0.91, 1.16)
Sugar-free beverages				
Model 1	0.36	0.32	0.38	0.36
	(0.28, 0.45)	(0.26, 0.39)	(0.29, 0.47)	(0.29, 0.43)
Model 2	0.38	0.33	0.38	0.35
	(0.29, 0.46)	(0.27, 0.39)	(0.29, 0.47)	(0.29, 0.42)
Model 3	0.39	0.34	0.37	0.34
	(0.31, 0.48)	(0.27, 0.40)	(0.28, 0.46)	(0.27, 0.41)
Breakfast consumption				
Model 1	4.98	4.11***	3.73***	3.18***
	(4.70, 5.25)	(3.88, 4.35)	(3.48, 3.98)	(2.97, 3.39)
Model 2	4.94	4.10***	3.72***	3.21***
	(4.66, 5.22)	(3.87, 4.33)	(3.48, 3.98)	(3.00, 3.42)
Model 3	4.99	4.11***	3.71***	3.19***
	(4.70, 5.27)	(3.87, 4.34)	(3.47, 3.96)	(2.97, 3.40)
Fast food consumption				
Model 1	1.43	1.51	1.73*	1.70*
	(1.26, 1.60)	(1.36, 1.66)	(1.54, 1.91)	(1.54, 1.86)
Model 2	1.46	1.52	1.73*	1.69
	(1.28, 1.63)	(1.37, 1.67)	(1.54, 1.91)	(1.53, 1.85)

Model 3	1.43 (1.26, 1.61)	1.51 (1.36, 1.66)	1.74* (1.55, 1.92)	1.70* (1.54, 1.86)
Sleep Quality[+]	Not at all	Somewhat	Very much	
N	604 (Referent)	811	358	
Caffeinated beverages				
Model 1	0.63 (0.55, 0.71)	0.72 (0.65, 0.80)	0.83** (0.71, 0.95)	
Model 2	0.70 (0.61, 0.79)	0.72 (0.64, 0.80)	0.73 (0.61, 0.85)	
Model 3	0.70 (0.62, 0.79)	0.72 (0.64, 0.80)	0.71 (0.59, 0.83)	
Sugar-sweetened beverages				
Model 1	0.82 (0.73, 0.92)	0.85 (0.75, 0.95)	1.06* (0.89, 1.22)	
Model 2	0.89 (0.78, 1.00)	0.85 (0.75, 0.94)	0.95 (0.79, 1.12)	
Model 3	0.89 (0.78, 1.00)	0.85 (0.75, 0.95)	0.94 (0.77, 1.10)	
Sugar-free beverages				
Model 1	0.30 (0.24, 0.35)	0.37 (0.31, 0.43)	0.42* (0.33, 0.52)	
Model 2	0.33 (0.27, 0.39)	0.36 (0.30, 0.41)	0.40 (0.30, 0.49)	
Model 3	0.33 (0.27, 0.39)	0.36 (0.31, 0.42)	0.39 (0.29, 0.48)	
Breakfast consumption				
Model 1	4.15 (3.93, 4.37)	3.99 (3.80, 4.16)	3.27** (3.02, 3.51)	
Model 2	4.04 (3.81, 4.27)	3.98 (3.80, 4.16)	3.42** (3.16, 3.68)	
Model 3	4.04 (3.81, 4.26)	3.98 (3.80, 4.16)	3.43** (3.17, 3.69)	
Fast food consumption				
Model 1	1.50 (1.36, 1.63)	1.64 (1.52, 1.76)	1.70 (1.49, 1.92)	

Model 2	1.59 (1.44, 1.74)	1.62 (1.50, 1.74)	1.60 (1.37, 1.82)
Model 3	1.59 (1.44, 1.74)	1.62 (1.50, 1.74)	1.60 (1.37, 1.82)

*p-value <0.05 **p-value <0.01
Model 1 adjusted for age, sex, race/ethnicity, education, marital status
Model 2 added depression, and physical activity
Model 3 added time in bed
Beverages measured in servings per day, breakfast and fast food servings per week
Caffeinated beverages were defined as low-calorie beverages with caffeine (e.g. Diet Coke, Diet Mountain Dew), carbonated beverages with caffeine and sugar (e.g., Coke, Pepsi, Mountain Dew, Dr. Pepper), tea with caffeine including green tea, coffee with caffeine, and dairy coffee drink (e.g. cappuccino)
¶Sugar-sweetened beverages were defined as carbonated beverages with caffeine and sugar, other carbonated beverages with sugar (e.g. 7-Up, Root Beer, Ginger Ale, Caffeine-Free Coke), and other sugared beverages (punch, lemonade, sports drinks, or sugared ice tea)
Sugar-free beverages were defined as low-calorie beverages with caffeine and other low-calorie beverages without caffeine (e.g. Diet 7-Up)
+Sleep quality was assessed via the following questions: During the past 12 months, how often have you been bothered or troubled by having trouble going to sleep or staying asleep

Table 2.3: Mean dietary intake (95% confidence interval) by sleep indices stratified by sex: Project-EAT

Time in Bed	<7 hours	7-8 hours	8-9 hours	>9 hours	P for interaction
Breakfast consumption					0.01
Men					
Model 1	3.90 (3.40, 4.39)	3.44 (3.14, 3.74)	3.83 (3.51, 4.15)	3.15 (2.76, 3.53)	
Model 2	3.78 (3.30, 4.25)	3.35 (3.05, 3.65)	3.71 (3.37, 4.04)	3.08 (2.70, 3.46)	
Women					
Model 1	3.49** (3.00, 3.98)	4.36 (4.05, 4.66)	4.23 (3.98, 4.49)	3.99 (3.65, 4.32)	
Model 2	3.60** (3.10, 4.10)	4.41 (4.11, 4.71)	4.28 (4.03, 4.53)	4.12 (3.78, 4.46)	
Sleep variability	< 0.5 hours	0.5 - <1 hour	1 – 1.5 hours	> 1.5 hours	P for interaction
Breakfast consumption					0.006
Men					
Model 1	3.84 (3.44, 4.25)	3.42 (3.06, 3.77)	3.75 (3.43, 4.08)	3.38 (3.02, 3.74)	
Model 2	3.71 (3.30, 4.12)	3.32 (2.97, 3.68)	3.66 (3.34, 3.99)	3.28 (2.93, 3.64)	
Model 3	3.75 (3.35, 4.16)	3.25 (2.89, 3.60)	3.63 (3.31, 3.95)	3.27 (2.92, 3.61)	
Women					
Model 1	3.77 (3.37, 4.16)	4.62** (4.29, 4.96)	4.10 (3.81, 4.39)	4.02 (3.73, 4.31)	
Model 2	3.83 (3.44, 4.21)	4.73*** (4.41, 5.06)	4.14 (3.85, 4.43)	4.15 (3.86, 4.44)	
Model 3	3.83 (3.44, 4.22)	4.73*** (4.41, 5.04)	4.12 (3.83, 4.41)	4.14 (3.84, 4.44)	
Sleep Timing					
Caffeinated beverages					0.0003
Men					
Model 1	0.43 (0.30, 0.55)	0.79*** (0.58, 0.82)	0.80*** (0.63, 0.97)	0.93*** (0.78, 1.07)	
Model 2	0.56 (0.41, 0.71)	0.76* (0.63, 0.89)	0.89** (0.72, 1.07)	0.97*** (0.82, 1.11)	
Model 3	0.60 (0.44, 0.75)	0.78 (0.65, 0.91)	0.89** (0.71, 1.06)	0.94** (0.80, 1.09)	
Women					
Model 1	0.70 (0.57, 0.84)	0.64 (0.51, 0.77)	0.67 (0.53, 0.81)	0.72 (0.60, 0.84)	
Model 2	0.67 (0.54, 0.81)	0.63 (0.50, 0.75)	0.61 (0.48, 0.75)	0.67 (0.55, 0.79)	
Model 3	0.68 (0.54, 0.81)	0.63 (0.50, 0.76)	0.62 (0.48, 0.76)	0.66 (0.54, 0.78)	
Sugar-free beverages					0.0005
Men					
Model 1	0.14 (0.06, 0.22)	0.32** (0.24, 0.41)	0.32** (0.23, 0.48)	0.39** (0.28, 0.49)	

Model 2	0.16	0.34**	0.38**	0.40***
	(0.08, 0.25)	(0.25, 0.44)	(0.24, 0.51)	(0.29, 0.50)
Model 3	0.20	0.35*	0.36*	0.37*
	(0.10, 0.29)	(0.25, 0.45)	(0.23, 0.49)	(0.27, 0.47)
Women				
Model 1	0.47	0.35	0.42	0.35
	(0.36, 0.57)	(0.26, 0.44)	(0.29, 0.55)	(0.26, 0.44)
Model 2	0.47	0.35	0.41	0.34
	(0.37, 0.58)	(0.26, 0.44)	(0.28, 0.53)	(0.25, 0.43)
Model 3	0.48	0.35	0.41	0.34
	(0.37, 0.58)	(0.26, 0.44)	(0.28, 0.53)	(0.24, 0.43)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Caffeinated beverages were defined as low-calorie beverages with caffeine (e.g. Diet Coke, Diet Mountain Dew), carbonated beverages with caffeine and sugar (e.g., Coke, Pepsi, Mountain Dew, Dr. Pepper), tea with caffeine including green tea, coffee with caffeine, and dairy coffee drink (e.g. cappuccino)

Sugar-free beverages were defined as low-calorie beverages with caffeine and other low-calorie beverages without caffeine (e.g. Diet 7-Up)

Table 2.4: Prevalence ratios (95% confidence intervals) for intake of energy drinks and sports drinks by sleep duration, variability, timing, and quality: Project EAT

Time in Bed	<7 hours	7-8 hours	8-9 hours	>9 hours
N	203	471	642	457
†Energy drinks				
Model 1	1.45 (0.95, 1.94)	Ref.	1.09 (0.79, 1.39)	1.03 (0.71, 1.35)
Model 2	1.39 (0.91, 1.87)	Ref.	1.08 (0.79, 1.38)	1.01 (0.71, 1.32)
†Sports drinks				
Model 1	0.97 (0.74, 1.20)	Ref.	0.86 (0.71, 1.02)	0.80* (0.62, 0.97)
Model 2	0.94 (0.71, 1.17)	Ref.	0.85* (0.70, 0.99)	0.80* (0.63, 0.98)
Sleep variability	< 0.5 hours	0.5 - <1 hour	1 – 1.5 hours	> 1.5 hours
N	339	364	571	500
Energy drinks				
Model 1	Ref.	1.59** (1.04, 2.14)	1.30 (0.88, 1.73)	1.40* (0.93, 1.87)
Model 2	Ref.	1.54* (1.02, 2.07)	1.29 (0.87, 1.70)	1.36 (0.90, 1.81)
Model 3	Ref.	1.52* (1.01, 2.04)	1.29 (0.87, 1.71)	1.35 (0.89, 1.81)
Sports drinks				
Model 1	Ref.	1.08 (0.84, 1.33)	1.01 (0.80, 1.23)	0.93 (0.71, 1.14)
Model 2	Ref.	1.06 (0.82, 1.30)	0.99 (0.79, 1.20)	0.92 (0.71, 1.13)
Model 3	Ref.	1.02 (0.79, 1.24)	0.95 (0.76, 1.15)	0.87 (0.68, 1.07)
Sleep Timing	≤ 10:30 PM	10:30-11:30 PM	11:30 PM-12:30 AM	> 12:30 AM
N	327	497	390	560
Energy drinks				
Model 1	Ref.	1.44 (0.86, 2.01)	1.63* (0.97, 2.29)	1.83** (1.10, 2.55)
Model 2	Ref.	1.36 (0.82, 1.90)	1.53* (0.92, 2.15)	1.71** (1.04, 2.38)
Model 3	Ref.	1.35 (0.82, 1.89)	1.50* (0.90, 2.11)	1.65** (0.99, 2.30)
Sports drinks				
Model 1	Ref.	1.07 (0.80, 1.34)	1.07 (0.79, 1.35)	1.22 (0.92, 1.51)
Model 2	Ref.	1.03 (0.78, 1.28)	1.04 (0.77, 1.30)	1.18 (0.90, 1.46)
Model 3	Ref.	1.01 (0.76, 1.26)	1.01 (0.75, 1.26)	1.15 (0.87, 1.43)
Sleep Quality⁺	Not at all	Somewhat	Very much	
N	604	811	358	
Energy drinks				

Model 1	Ref.	1.42**	1.96***
		(1.06, 1.78)	(1.40, 2.51)
Model 2	Ref.	1.38*	1.86***
		(1.01, 1.75)	(1.29, 2.42)
Model 3	Ref.	1.37*	1.79***
		(1.01, 1.74)	(1.24, 2.34)
Sports drinks			
Model 1	Ref.	1.00	1.24*
		(0.83, 1.17)	(0.99, 1.49)
Model 2	Ref.	0.99	1.28*
		(0.82, 1.17)	(1.00, 1.55)
Model 3	Ref.	1.00	1.28*
		(0.83, 1.18)	(1.00, 1.56)

*p-value <0.05 **p-value <0.01
Model 1 adjusted for age, sex, race/ethnicity, education, marital status
Model 2 added depression, and physical activity
Model 3 added sleep duration
[+]Sleep quality was assessed via the following questions: During the past 12 months, how often have you been bothered or troubled by having trouble going to sleep or staying asleep?
[†]Energy and sports drink consumption defined as ≥ one drink per week compared to < one drink per week

Supplemental Table 2.1: Mean dietary intake by categories of sleep duration, with the inclusion of a <6 hours/night category: Project EAT

Time in Bed	<6 hours	6-7 hours	7-8 hours	8-9 hours	>9 hours
N	59	144	471 (Referent)	642	457
Caffeinated drinks					
Model 1	1.01* (0.70, 1.33)	0.82 (0.62, 1.01)	0.66 (0.57, 0.75)	0.68 (0.60, 0.77)	0.74 (0.63, 0.85)
Model 2	0.94 (0.62, 1.25)	0.85 (0.65, 1.04)	0.67 (0.58, 0.76)	0.70 (0.61, 0.78)	0.71 (0.61, 0.82)
Sugar-sweetened beverages					
Model 1	1.29 (0.85, 1.74)	0.86 (0.67, 1.06)	0.85 (0.74, 0.97)	0.83 (0.73, 0.93)	0.94 (0.79, 1.09)
Model 2	1.22 (0.78, 1.65)	0.89 (0.70, 1.09)	0.86 (0.74, 0.98)	0.85 (0.75, 0.94)	0.91 (0.76, 1.05)
Sugar-free beverages					
Model 1	0.39 (0.16, 0.61)	0.51 (0.32, 0.69)	0.36 (0.29, 0.43)	0.33 (0.28, 0.39)	0.33 (0.26, 0.40)
Model 2	0.36 (0.13, 0.58)	0.51 (0.33, 0.70)	0.36 (0.29, 0.43)	0.34 (0.28, 0.40)	0.32 (0.25, 0.39)
Breakfast consumption					
Model 1	3.20* (2.60, 3.79)	4.01 (3.56, 4.46)	3.94 (3.72, 4.16)	4.07 (3.87, 4.27)	3.65 (3.39, 3.92)
Model 2	3.33 (2.74, 3.92)	3.95 (3.51, 4.38)	3.92 (3.70, 4.14)	4.04 (3.84, 4.24)	3.69 (3.43, 3.95)
Fast food consumption					
Model 1	1.69 (1.08, 2.30)	1.50 (1.18, 1.83)	1.53 (1.38, 1.69)	1.58 (1.45, 1.71)	1.72 (1.56, 1.89)
Model 2	1.59 (1.02, 2.16)	1.54 (1.21, 1.87)	1.55 (1.39, 1.70)	1.60 (1.47, 1.73)	1.71 (1.54, 1.88)

* $p < 0.05$
Model 1 adjusted for age, sex, race/ethnicity, education, marital status
Model 2 added depressive symptoms and physical activity

Supplemental Table 2.2: Prevalence ratios for intake of energy drinks and sports drinks by sleep duration with the inclusion of a <6 hours/night category: Project EAT

Time in Bed	<6 hours	6-7 hours	7-8 hours	8-9 hours	>9 hours
N	59	144	471	642	457
†Energy drinks					
Model 1	1.55	1.41	Ref.	1.09	1.03
	(0.59, 2.50)	(0.90, 1.92)		(0.79, 1.39)	(0.72, 1.35)
Model 2	1.44	1.37	Ref.	1.08	1.01
	(0.54, 2.34)	(0.86, 1.87)		(0.79, 1.38)	(0.71, 1.32)
†Sports drinks					
Model 1	1.12	0.91	Ref.	0.86	0.80*
	(0.69, 1.56)	(0.66, 1.16)		(0.71, 1.02)	(0.62, 0.98)
Model 2	1.11	0.88	Ref.	0.85*	0.80*
	(0.67, 1.55)	(0.63, 1.12)		(0.70, 0.99)	(0.63, 0.98)

*p-value <0.05
Model 1 adjusted for age, sex, race/ethnicity, education, marital status
Model 2 added depressive symptoms and physical activity
†Energy and sports drink consumption defined as ≥ one drink per week compared to < one drink per week

Chapter 3: Manuscript 2 - Actigraphy-measured sleep indices and adiposity: the Multi-Ethnic Study of Atherosclerosis

This paper has been published in the journal *Sleep* and a PDF has been included as an attachment.

Citation: Ogilvie RP**,** Redline S, Bertoni AG, Chen X, Ouyang P, Szklo M, Lutsey PL. Actigraphy measured sleep indices and adiposity: The Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep* 2016;39(9):1701-1708.

Abstract

Study Objectives: To investigate the cross-sectional relationship between objectively measured sleep characteristics and multiple indices of adiposity in racially/ethnically diverse older adults within the MESA Sleep study (n = 2,146).

Methods: 7-day actigraphy was used to assess sleep duration, sleep efficiency, and night-to-night variability. Body mass index (BMI), waist circumference, and total body fat were modeled continuously and according to obesity cut-points. Models were adjusted for demographic, socioeconomic, and behavioral variables.

Results: Participants who slept less than 6 hours a night had significantly higher BMI, waist circumference, and body fat relative to those who slept 7-8 hours. Those who slept less than 5 hours had a 16% higher prevalence of general obesity (BMI ≥30 vs. <25 kg/m^2) (95% [CI]: 0.08-0.24) and a 9% higher prevalence of abdominal obesity (waist

circumference: women ≥88 centimeters, men ≥102 centimeters; 95% CI: 0.03-0.16) compared to those who slept 7-8 hours. Results were similar for sleep efficiency and night-to-night sleep variability.

Conclusions: Among an older multi-ethnic cohort, we found robust associations across multiple indices of sleep and adiposity. Targeting sleep characteristics may be of benefit in obesity interventions, but more research is needed to rule out reverse causality.

Introduction

According to the most recent data, 69.2% of Americans self-reported that they did not get enough sleep at least one day in the previous month,[245] and 68.5% of American adults were overweight or obese (2011-2012).[246] Because the prevalence of these conditions is high, Healthy People 2020 objectives include increasing the proportion of adults who get sufficient sleep and are at a healthy weight.[2] These co-occurring high prevalences, together with pathophysiologic evidence,[152] have suggested that sleep and obesity are interrelated. Although there is a strong inverse association between sleep and obesity in children,[247] the relationship is less consistent in adults, and studies have reported inverse associations, U-shaped associations, or no association.[138-141,202] Most studies, however, have used self-reported measures of sleep duration, only one measure of obesity, and racially/ethnically homogenous populations.

Literature on other measures of sleep, such as sleep efficiency and night-to-night sleep variability, is more limited because it cannot be assessed well with self-report measures. Previous studies have found that lower sleep efficiency and higher sleep variability are associated with higher levels of obesity.[236,248,249]

The Multi-Ethnic Study of Atherosclerosis (MESA) provides an opportunity to evaluate the relationship between actigraphy-measured sleep indices and multiple measures of adiposity in a racially diverse population. We hypothesized that short sleep duration, low sleep efficiency and high sleep duration variability will be associated with higher levels of adiposity independently of other confounders. We also evaluated whether the association differed by age, sex, or race/ethnicity.

Methods

MESA is a cohort study designed to study risk factors for clinical and subclinical cardiovascular diseases in four racial/ ethnic groups.[250] The study began in July 2000 and recruited 6,814 adults free of clinical CVD and aged 45-84 years from 6 field centers across the United States: Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; Saint Paul, MN; and Winston-Salem, NC. Five exams have now taken place, with the most recent occurring from April 2010 to February 2013. All of the 4,077 participants who attended Exam 5 were approached for participation in MESA Sleep, an ancillary study of objective measures of sleep and their relationship to cardiovascular disease. The median time interval between Exam 5 and MESA Sleep was 301 days (range 0-1024 days). Sleep data was received from 2,261 participants, and the current cross-sectional analysis included 2,146 participants with data on both sleep and adiposity measures. Local institutional review boards approved study protocols, and all participants gave written informed consent.

Exposures

Sleep measures were assessed using at home 7-day actigraphy. All participants wore the Actiwatch Spectrum wrist actigraph (Philips Respironics, Murrysville, PA) on the non-dominant wrist. Output was scored by a certified technician using an event marker, a self-reported sleep diary, and data on light levels at the Sleep Reading Center at Brigham and Women's Hospital in Boston, Massachusetts.[13] Sleep interval start and end time were determined by activity count increases and decreases, respectively. These times were compared to the event marker, sleep journal bed and wake times, and light

level changes. The Cole-Kripke algorithm was used to generate data on sleep duration and sleep efficiency.[251] Sleep duration was defined as the average sleep time in main sleep periods across all days, defined as the sum of the sleep time over each night divided by the total number of days. This variable was modeled in 5 categories: <5 h, 5-6, 6-7, 7-8, and >8 hours. Sleep efficiency was defined as the percentage of time spent asleep in the sleep interval ("lights off" to "lights on"). For modeling purposes, we first categorized sleep efficiency according to quartiles of the distribution, then we further divided the lowest category according to the commonly used threshold of less than 85. The 5 categories were then <85%, 85-87.9%, 87.9-90.4%, 90.4%-92.4%, and >92.4%. Night-to-night variability in sleep duration was measured in minutes using the within person between-night standard deviation (SD) of the sleep duration variable, and was modeled in approximate quartiles (≤48, 48-70, 70-99, and 99-262).

Outcomes

All measures of adiposity were obtained during the MESA Exam 5 clinic visits. Participants wore light clothing and no shoes. Height was measured to the nearest 0.5 cm using an Accu-Hite measure device and weight was measured to the nearest 0.5 kg using a Detecto Platform Balance Scale. BMI was calculated in kg/m^2. Waist circumference was measured at the umbilicus to the nearest 0.1 cm using a Gulick II 150 cm anthropometric tape. Total body fat was measured in kilograms via full body bioelectrical impedance analysis (BIA) using the Valhalla BCS-2 Body Composition scale and printer. In validation studies, bioelectrical impedance was highly correlated with dual-energy X-ray absorptiometry and was a much better estimator of body fat than BMI.[252]

Covariates

Additional information on sociodemographics and behaviors was assessed via questionnaire at Exam 5. Alcohol use was characterized as present drinking of alcoholic beverages or not. Smoking status was categorized as current, former, or never smoker. Depressive symptoms were assessed with the Center for Epidemiological Studies Depression Scale (CES-D) and was modeled dichotomously with a cutpoint at 16; scores at this point or higher are typically indicative of clinically significant symptomatology.[253] Antidepressant use was categorized as yes based on use of tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and other depressants. Sleeping pill use was categorized as no use in the past 4 weeks, less than once a week, 1 or 2 times a week, 3 or 4 times a week, or ≥5 times a week. Sleep apnea was measured using in-home overnight polysomnography, as has been previously described.[13] It included all central and obstructive apneas and hypopneas ≥4% desaturation and was modeled in 4 categories according to apnea-hypopnea index: 0 to <5, 5 to <15, 15 to <30, and 30+ per night.

Analysis

Descriptive statistics were calculated for the exposure variables, stratified by sleep duration category. We used linear regression and logistic regression to model the relationship between the sleep indices and each anthropometric measure. Outcome measures were modeled both as continuous variables (linear regression) and according to dichotomous categories (logistic regression). Using the margins command in Stata, adjusted probabilities standardized to the total population were calculated for each

category of the sleep exposure in the logistic models, and these probabilities were used to calculate prevalence differences for each obesity outcome.[254] In the models with dichotomized outcomes, cutoffs for each measure were chosen according to standard guidelines. Participants with a BMI ≥30 kg/m^2 were categorized as having overall obesity, those with a BMI between 25 and 29.9 kg/m^2 were categorized as overweight, and those with a BMI <25 kg/m^2 were categorized in the normal weight reference group. Abdominal obesity was defined as ≥88 cm for women and ≥102 cm for men.

We explored a series of models. The first model controlled for age, field center, race/ethnicity, and sex. Model 2 added socioeconomic and behavioral variables, including marital status, income, education, smoking, depressive symptoms, sleeping pill use, and alcohol use. Model 3 included covariates in Model 2 plus sleep apnea. For models with sleep efficiency and night-to-night variability as an exposure, we also adjusted for sleep duration (Model 4). Interactions between sleep and age, sex, and race/ethnicity on indices of adiposity were tested using cross-product terms in the linear models and stratified results were reported, as appropriate. Sensitivity analyses excluded individuals with long sleep (duration >9 h) or sleep apnea (AHI ≥15).

Results

The mean age in the analytic sample was 68.6 (SD 9.2) years, and 53.7% were female. Mean hours of sleep were 6.5 (SD 1.4). The mean BMI in the sample was 28.8 (SD 5.6), and mean waist circumference was 99.7 cm (SD 14.5); these indicators were approximately normally distributed. Indices of adiposity varied by race/ethnicity; general obesity (BMI ≥30 kg/m^2) was present in 30.1% of whites, 49.2% of African Americans,

4.9% of Chinese, and 44.3% of Hispanics. For abdominal obesity (waist circumference: women ≥88 cm, men ≥102 cm) these proportions were 56.7%, 69.9%, 27.1%, and 65.0%, respectively.

Table 3.1 shows sociodemographic and behavioral characteristics by sleep duration category. Those averaging <5 h of sleep per night were more likely to be male, African American, and current smokers. There was also important variation by race/ ethnicity, with a range of 7.9% (whites) to 20.8% (African Americans).

Table 3.2 shows adjusted means of adiposity measures by categories of the sleep indices from the linear models. Overall, we found significant associations between each sleep exposure and BMI, waist circumference, and total body fat. For example, after accounting for demographics, BMI was 1-2 units larger among those with short sleep duration (<5 h), low sleep efficiency, or high sleep variability relative to those who slept 7-8 h/night, had high sleep efficiency, or low sleep variability, respectively. Similar results were found for waist circumference and total body fat, where those with short sleep duration, low sleep efficiency, or high sleep variability had a waist circumference 2.5 to 5 cm larger and body fat 2 to 3 kg more than those who slept 7-8 h/night, had high sleep efficiency, or low sleep variability. Further adjustment for socioeconomic and behavioral variables did not significantly alter the estimates, though the effect of sleep efficiency and variability was reduced with adjustment for sleep duration. Models where each exposure was treated continuously per one standard deviation can be found in **Supplemental Table 3.1**. Results were similar to the exposures modeled categorically. Results were also similar in sensitivity analyses when we removed from the analysis the

41 individuals who slept >9 h/night (data not shown). Associations were attenuated, but some retained statistical significance, when sleep apnea was added into the model and when analyses were restricted to those with AHI<15 (**Table 3.2** and **Supplemental Table 3.2**).

Effect modification by age, sex, and race/ethnicity was also tested in each linear model. Significant interaction terms were found between sleep efficiency and sex for each outcome; sex-stratified results are presented in **Supplemental Table 3.3**. Across sleep efficiency categories, men had similar BMIs, while for women lower sleep efficiency was associated with higher BMI. Similar results were found for waist circumference, where men had similar waists across sleep efficiency categories, but for women lower sleep efficiency was associated with higher waist circumference. Significant interaction terms were also found between age (dichotomized at the median) and sleep efficiency when waist circumference was the outcome ($p = 0.03$). Across sleep efficiency categories, those over age 68 had similar waists, while for those younger than 68, lower sleep efficiency was associated with higher waist circumference (**Supplemental Table 3.4**). Although interactions terms approached significance for sex and sleep duration when the outcomes were BMI and waist circumference, no major differences between men and women were detected (**Supplemental Table 3.5**). No significant interactions were found between sleep variability and the adiposity outcomes. Additionally, no significant interactions were found by race/ethnicity for any of the exposures or outcomes.

Figure 3.1 shows the prevalence differences for models with dichotomous outcomes. After accounting for demographics, those who slept <5 h/night had a 16% higher prevalence of obesity (BMI ≥30 vs. <25 kg/m^2; P < 0.001) and a 7% higher prevalence of overweight (P = 0.133) compared to those who slept 7-8 h/night (Fig. 3.1, Panel A; Supplemental Table 3.6). They also had a 10% higher prevalence of abdominal obesity (defined as waist circumference ≥102 cm in men, ≥88 cm in women) (P = 0.002). Participants with lower sleep efficiency tended to be more obese by all definitions, though associations did not always achieve statistical significance (Fig. 3.1, Panel B). Those in the highest quartile of sleep variability had a 5% higher prevalence of general obesity (P = 0.167) and a 6% higher prevalence of abdominal obesity (P = 0.037) compared to those in the lowest quartile (Fig. 3.1, Panel C). For all exposures, further adjustment for socioeconomic and behavioral variables slightly reduced the estimates, while adjustment for sleep apnea resulted in substantial attenuation (Supplemental Tables 3.6, 3.7).

Discussion

In this older, multi-racial/ethnic population of 2,146 adults from the MESA study, we found robust evidence that actigraphy measured sleep characteristics are cross-sectionally associated with several markers of adiposity. Those sleeping less than 5 hours per night had higher BMIs, larger waists, and more kilograms of body fat than those who slept 7-8 hours a night. Those with low sleep efficiency and high sleep variability also had higher BMIs, larger waists, and more body fat. Effects were smaller for sleep efficiency and variability once sleep duration was considered. There was also some

evidence that effects were stronger in women compared to men, and for younger compared to older participants.

Previous research examining the cross-sectional relationship between sleep and obesity in adults has mainly focused on sleep duration, and has found a variety of different associations, including inverse, U-shaped, and no association.[138,139,202] The majority of these studies use self-report questionnaires to assess sleep duration.[255] Notably, self-reported and objectively measured sleep are only moderately correlated, and discrepancies between the two are related to a variety of pertinent confounders.[22,256] Studies that did use objective measures of sleep duration also had mixed results with some finding inverse and U-shaped associations.[132,248,257] Importantly, the only two longitudinal studies on this topic that used objective sleep measures found no association,[132,258] which may suggest that this relationship is not causal in adults. Prospective studies using self-reported sleep data have found inverse, U-shaped, and no associations.[202,255,259,260] However, there is strong and consistent evidence for a causal association between sleep duration and obesity among children and adolescents,[139,261] including findings from a randomized crossover trial.[262] More longitudinal and experimental studies with standardized measures are needed to determine whether the association between short sleep duration and adiposity is causal in adults.

Because few published studies used actigraphy, most did not evaluate the relationship between sleep efficiency, sleep variability, and obesity. Previous research has found that low sleep efficiency and high sleep variability are associated with both general and abdominal obesity.[236,248,249] Better characterizing the associations between

specific sleep disturbances, such as those that relate to short sleep duration vs. inconsistent sleep patterns, may be useful when designing future interventions.

In this study, the relationship between actigraphy-measured sleep characteristics and obesity was substantially attenuated with both adjustment for sleep apnea and restriction to those without sleep apnea. Few studies on sleep duration and obesity have examined sleep apnea because most relied on self-reported measures of sleep duration. Those that have examined it found that the relationship between sleep duration and obesity remained even after adjustment for OSA.[258] The causal pathways between sleep duration, sleep apnea, and obesity are complicated. Obesity has been strongly and consistently associated with sleep apnea, with randomized trials of weight loss demonstrating that weight loss is causally associated with a reduction in AHI.[86] It has also been suggested that weight loss may increase sleep duration through attenuating sleep apnea. However, the current evidence to support this hypothesis is limited and inconsistent, finding null or small associations.[263-265] Patients with sleep apnea treated with CPAP may actually gain weight.[266] Because the direction and strength of these relationships is complex, models with adjustment for sleep apnea require careful interpretation. More research is needed to disentangle the components of the relationship between sleep characteristics, sleep apnea, and obesity.

There are several potential pathways through which sleep indices can influence obesity.[152] One possible mechanism is that short sleep duration may lead to increased food intake. Experimental studies have demonstrated that short sleep can lead to both self-reported and biological changes in hunger and appetite, including increases in ghrelin

and decreases in leptin.[139,153] Recent brain imaging data also suggest that insufficient sleep may increase central neuronal responses to high caloric foods, increasing behaviors leading to overeating.[154] With more hours available in the day, short sleepers may also have more opportunities to eat. In another potential pathway, lack of sleep may lead to fatigue, which can lead to decreased physical activity. Pathways for efficiency and variability are less clear, but likely act through similar mechanisms. People with low sleep efficiency also may have selective deprivation of deep sleep (stage N3), which has been linked to central obesity,[267] likely through effects on the hypothalamic pituitary adrenal axis and the autonomic nervous system.[268] People with high sleep variability may represent those who engage in short sleep certain nights of the week and then compensate on other nights. Additionally, those with high sleep variability may have irregular eating patterns due to variation in their sleep-wake pattern.[236] Thus, sleep variability may increase risk of adiposity through exposure to both periodic insufficient sleep, as well as by contributing to irregularity in the synchronization of eating and sleep timing, which is increasingly recognized to be important in energy balance.[236]

Existing studies of sleep and obesity have often relied on BMI as the sole measurement of the adiposity. Although BMI is easy to measure, it does not differentiate between lean and fat mass. Other measures, such as waist circumference better quantify the distribution of body fat. Studies that have examined sleep duration and other measures of adiposity have found inverse associations though there were some differences by sex.[248,269,270] In this study, we measured adiposity with BMI, waist

circumference, and total body fat measured through full body bioelectrical impedance and found that all behaved similarly within each sleep measure.

Prior research on sleep and obesity has also been conducted in mostly Caucasian populations. In our sample, as has been shown by others,[33,40] minority groups slept for a shorter duration compared to white populations. Likewise, in our population, as is well established,[271] obesity varied by race/ ethnicity. However, in our sample the relationship between sleep duration and efficiency with obesity was not modified by race. This is consistent with a National Health and Nutrition Examination Survey analysis of whites, African Americans and Mexican Americans, which found an inverse linear association between self-reported sleep duration and obesity that did not vary by race/ ethnicity.[270] Notably, the Insulin Resistance Atherosclerosis Study (IRAS) previously reported that among 332 Hispanic and 775 African American participants, a U-shaped association was observed between self-reported sleep duration and change in adiposity, though only among participants less than 40 years old.[259] Additional studies conducted in racially/ ethnically diverse populations are needed to make more definitive conclusions.

However, we did find effect measure modification by sex and age. Our finding that the relationship between sleep efficiency and obesity was stronger in women than men has been reported by others.[236,248] In the current study, we also found effect modification by age for the relationship between sleep efficiency and waist circumference, whereby the association was stronger among younger individuals. More studies are needed to confirm this finding.

This study has several strengths. The use of actigraphy instead of self-reported sleep duration resulted in less measurement error of the exposure, and allowed for the ascertainment of both sleep efficiency and sleep variability. However, actigraphy has high sensitivity and low specificity because it detects wakefulness less accurately. Another strength of this study is its use of multiple measures of adiposity, instead of relying solely on BMI. The study also uses a population-based sample of four different racial/ethnic groups instead of a homogenous population.

This study also has several weaknesses. Foremost, no single observational study, particularly a cross-sectional one, allows establishing causality. Since measures of sleep and obesity were taken at the same time, temporality cannot be determined so the possibility of reverse causation exists. Because the pathway between sleep duration and obesity is not fully understood, it is possible that we neglected to control for all confounders. Additionally, residual confounding may have remained despite our attempts at adjustment.

Overall, this cross-sectional study found associations between multiple measures of objectively measured sleep and adiposity. The National Sleep Foundation presently recommends that adults aged 26-64 years get 7 to 9 hours of sleep per night, and that adults aged 65 or older get 7 to 8 hours of sleep per night.[272] If short sleep is causally associated with the development of obesity in adults, as it is believed to be in children,[262,273] increasing sleep duration among individuals with short sleep could represent an important public health intervention because a large proportion of the US population reports short sleep,[274] and this is especially true among African Americans

and Hispanics.[33,40] Our study also identifies the potential importance of sleep efficiency and sleep variability as contributors to obesity. Future interventions that target one of more of these sleep traits in obesity prevention programs may yield novel insights into approaches for achieving the Healthy People 2020 health objectives.

Table 3.1: Participant characteristics by sleep duration category: The MESA Study 2010-2013

	<5 hours	5-6 hours	6-7 hours	7-8 hours	>8 hours
N total	284	388	679	559	241
Demographics					
Age, mean years ± SD	69.5 ± 9.9	67.9 ± 8.9	67.8 ± 8.9	68.3 ± 9.1	72.2 ± 9.3
% Female, n (%)	104 (36.6)	197 (50.8)	352 (51.8)	347 (62.1)	155 (64.3)
Race/Ethnicity, n (%)*					
White/Caucasian	64 (7.9)	93 (11.5)	266 (33.0)	267 (33.1)	116 (14.4)
Chinese American	40 (16.4)	50 (20.5)	70 (28.7)	66 (27.1)	18 (7.4)
Black/ African American	124 (20.8)	140 (23.5)	191 (32.0)	100 (16.8)	42 (7.0)
Hispanic	56 (11.1)	105 (20.8)	152 (30.2)	126 (25.0)	65 (12.9)
Education, n (%)					
< High school	39 (13.8)	52 (13.4)	90 (13.3)	79 (14.2)	52 (21.6)
High school	48 (17.0)	76 (19.6)	104 (15.3)	91 (16.3)	38 (15.8)
> High school	196 (69.3)	260 (67.0)	484 (71.4)	387 (69.5)	151 (62.7)
Married, n (%)	151 (54.5)	209 (54.6)	434 (64.7)	354 (63.9)	128 (54.5)
Behavioral Characteristics					
Sleeping pill use 5+ times a week, n(%)	17 (6.1)	19 (5.0)	39 (5.8)	43 (7.7)	18 (7.5)
Smoking, n (%)					
Current	35 (12.5)	31 (8.1)	46 (6.8)	23 (4.1)	21 (8.8)
Former	136 (48.4)	172 (44.7)	304 (45.0)	274 (49.1)	101 (42.3)
Never	110 (39.2)	182 (47.3)	326 (48.2)	261 (46.8)	117 (49.0)
Presently drinking alcohol, N (%)	112 (39.9)	152 (39.5)	314 (46.4)	263 (47.1)	88 (36.8)
CES-D ≥16, n (%)	51 (18.5)	73 (19.1)	83 (12.4)	68 (12.3)	37 (15.7)
Outcomes, mean ± SD					
Body mass index (kg/m^2)	29.9 ± 5.7	29.4 ± 5.8	28.8 ± 5.6	28.1 ± 5.4	28.1 ± 5.3
Waist	103.1 ±	101.1 ±	99.6 ±	97.4 ±	98.7 ± 14.6

circumference (cm)	14.4	14.9	14.6	13.8	
Total body fat (kg)	26.3 ± 11.6	25.9 ± 11.3	25.0 ± 11.0	24.4 ± 10.6	25.2 ± 10.9
BMI ≥30, n(%)	128 (45.2)	149 (38.5)	243 (35.8)	175 (31.4)	75 (31.4)
BMI 25-29.9, n(%)	99 (35.0)	159 (41.1)	250 (36.8)	211 (37.8)	87 (36.4)
Abdominal obesity, n(%)	176 (62.2)	235 (60.7)	388 (57.1)	319 (57.3)	146 (61.3)

* Percentages represent row percentages

Abbreviations: CES-D, Center for Epidemiological Studies-Depression; SD, standard deviation.

Table 3.2: Adjusted means of adiposity measures by categories of sleep duration, efficiency and variability: The Multi-Ethnic Study of Atherosclerosis 2010-2013

Sleep Duration	<5 hours	5-6 hours	6-7 hours	7-8 hours (Referent)	>8 hours	P for linear trend
N	288	388	679	559	241	
BMI (kg/m^2)						
Model 1	30.1***	29.3**	28.7	28.2	28.2	<0.001
Model 2	30.1***	29.5 ***	28.7	28.2	28.3	<0.001
Model 3	29.4**	29.4**	28.9	28.3	28.1	<0.001
Waist circumference (cm)						
Model 1	102.7***	100.9**	99.4	98.0	98.7	<0.001
Model 2	102.2***	101.2**	99.6	98.0	98.9	<0.001
Model 3	100.9*	101.0**	99.8*	98.2	98.3	0.001
Total body fat (kg)						
Model 1	27.4***	25.9*	25.0	24.3	24.2	<0.001
Model 2	27.3***	26.1*	25.1	24.4	24.3	<0.001
Model 3	26.1*	26.1*	25.4	24.5	23.9	0.002
Sleep Efficiency	<85%	85-87.9%	87.9-90.4%	90.4%-92.4%	>92.4% (Referent)	
N	208	329	544	523	547	
BMI (kg/m^2)						
Model 1	29.3**	29.5***	28.8*	28.7	28.2	<0.001
Model 2	29.2*	29.6**	29.0*	28.7	28.3	0.001
Model 3	28.8	29.4**	28.9	28.8	28.3	0.028

Model 4	28.6	29.3*	28.9	28.9	28.4	0.171
Waist Circumference (cm)						
Model 1	101.4**	101.4***	99.6*	99.8*	97.9	<0.001
Model 2	100.9*	101.6**	99.8*	99.8*	98.1	0.001
Model 3	100.0	101.0**	99.7*	100.2*	98.0	0.015
Model 4	99.5	100.8*	99.7	100.2*	98.2	0.080
Total Body Fat (kg)						
Model 1	26.3**	26.6***	25.4**	25.3*	23.8	<0.001
Model 2	26.0*	26.6 ***	25.6*	25.2	24.0	0.001
Model 3	25.3	26.3**	25.4*	25.5*	24.1	0.020
Model 4	24.9	26.2*	25.3	25.5	24.3	0.105
Sleep duration Variability	≤48 (Referent)	48-70	70-99	99-262		
N	535	554	523	539		
BMI (kg/m^2)						
Model 1	28.3	28.7	29.0*	29.2**		0.004
Model 2	28.4	28.8	29.0	29.3**		0.003
Model 3	28.4	28.8	28.8	29.2*		0.026
Model 4	28.6	28.8	28.8	29.0		0.220
Waist Circumference (cm)						
Model 1	98.1	99.5	100.3*	100.7**		0.002
Model 2	98.3	99.6	100.2*	101.0**		0.002

Model 3	98.5	99.7	99.7	100.5*	0.026
Model 4	98.8	99.8	99.6	100.2	0.171
Total Body Fat (kg)					
Model 1	24.2	24.9	25.7*	26.0**	0.001
Model 2	24.3	25.0	25.7*	26.3**	0.001
Model 3	24.5	25.0	25.4	26.0*	0.015
Model 4	24.7	25.0	25.3	25.8	0.098

Sleep duration variability is defined as the within-person standard deviation of sleep duration and is measured in minutes
*P < 0.05, **P < 0.01, ***P < 0.001

Model 1 adjusted for age, sex, race, and field center

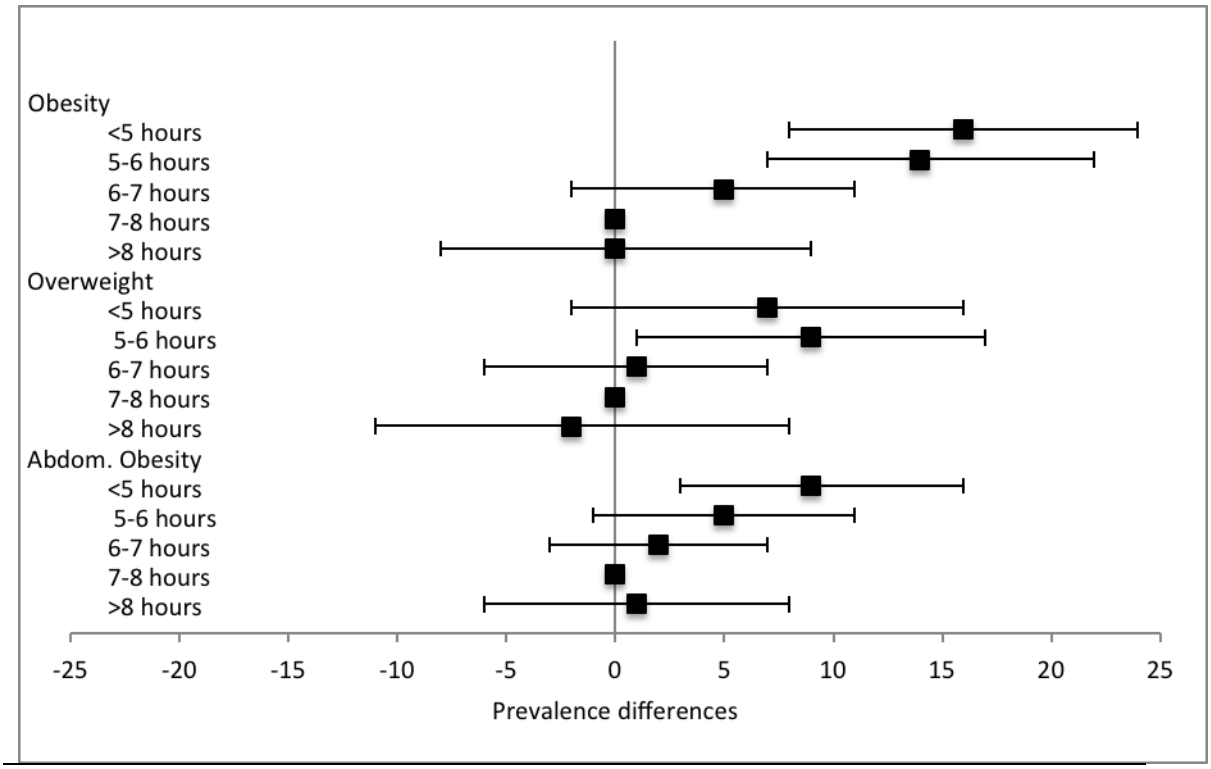
Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education

Model 3 adjusted for model 2, plus sleep apnea

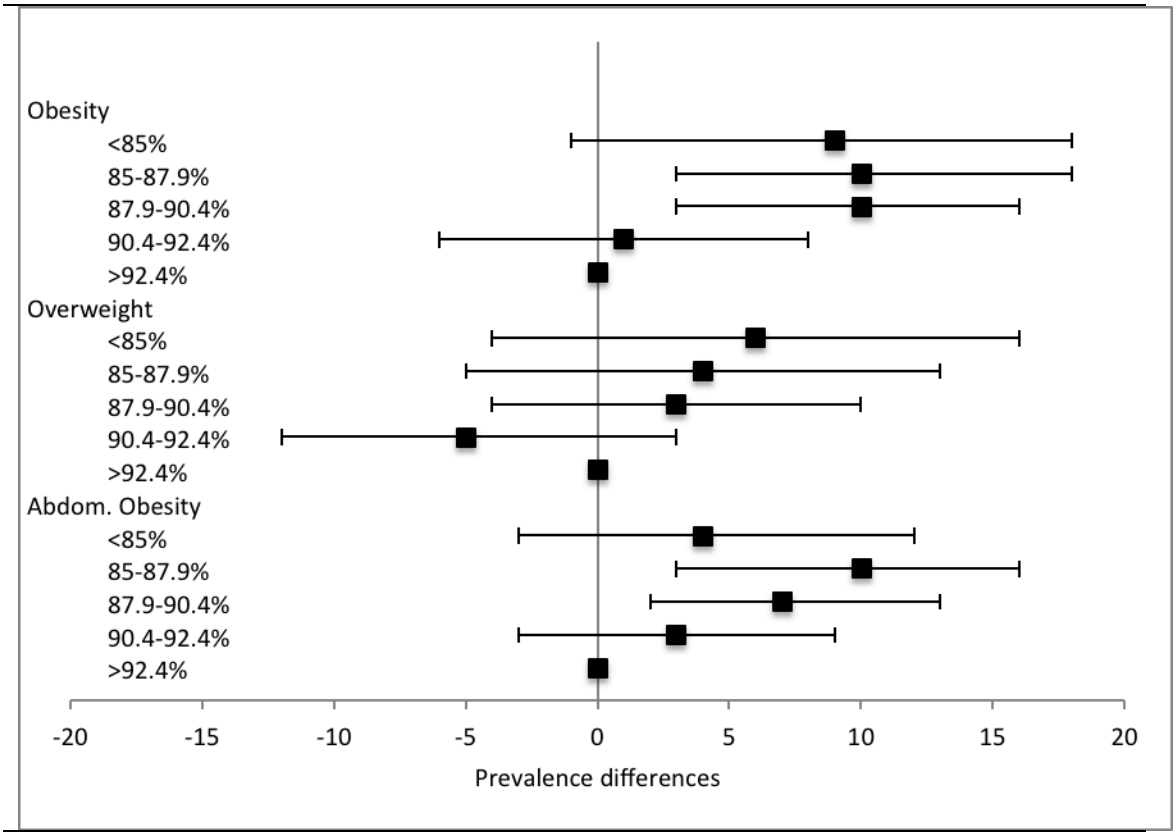
Model 4 adjusted for model 3, plus sleep duration

Figure 3.1: Prevalence differences* for obesity, overweight, and abdominal obesity by sleep duration, sleep efficiency, and sleep variability

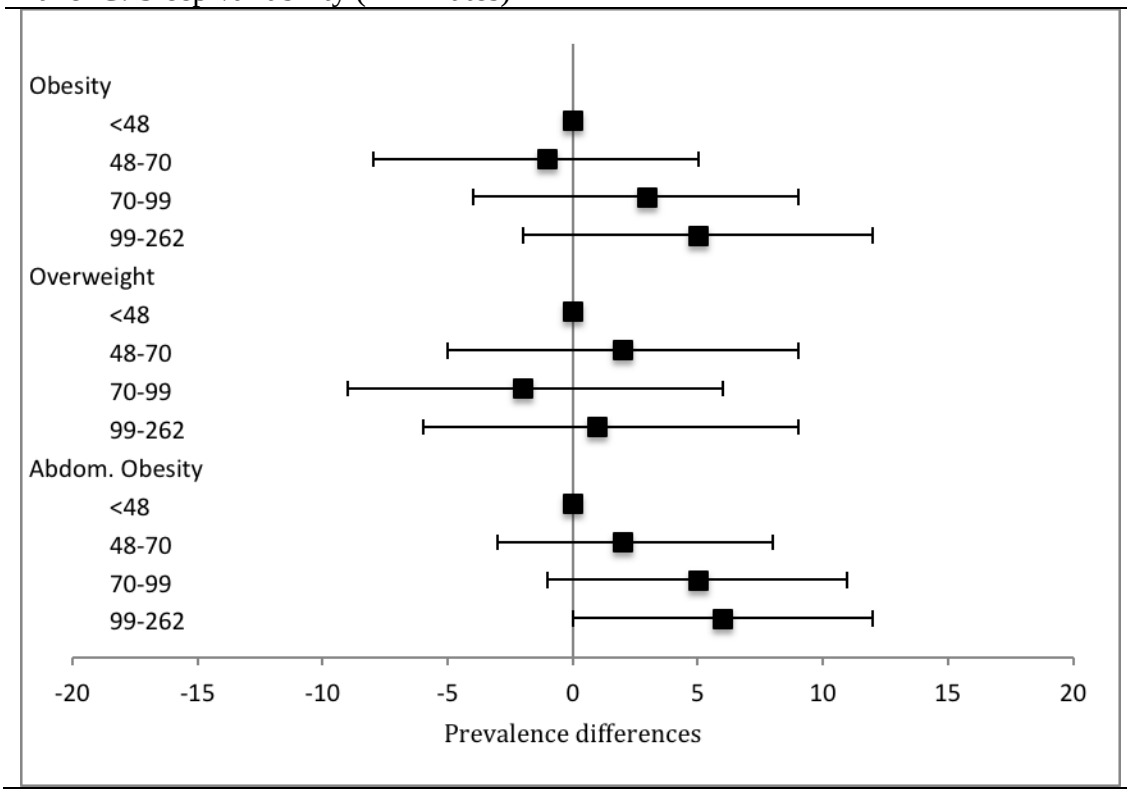
Panel A: Sleep duration



Panel B: Sleep efficiency



Panel C: Sleep variability (in minutes)



* Interpretation: Sleeping less than five hours per night was associated with an additional 16 cases of obesity per 100 individuals studied.
Models adjusted for age, sex, race, field center, depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education
Obesity was defined as ≥30 kg/m^2, overweight was defined as 25-29.9 kg/m^2, abdominal obesity was ≥88 cm for women and ≥102 cm for men

Supplemental Table 3.1: Adiposity measures by continuous sleep duration, efficiency, and variability per 1 SD: The Multi-Ethnic Study of Atherosclerosis 2010-2013

	Sleep Duration		Sleep Efficiency		Sleep Duration Variability	
	Continuous per 1 SD	P for linear trend	Continuous per 1 SD	P for linear trend	Continuous per 1 SD	P for linear trend
BMI (kg/m^2)						
Model 1	-0.58	<0.001	-0.45	<0.001	0.29	0.012
Model 2	-0.56	<0.001	-0.43	<0.001	0.34	0.005
Model 3	n/a		-0.33	0.008	0.23	0.062
Waist circumference (cm)						
Model 1	-1.30	<0.001	-1.27	<0.001	0.84	0.005
Model 2	-1.17	<0.001	-1.21	<0.001	0.94	0.003
Model 3	n/a		-1.00	0.002	0.73	0.025
Total body fat (kg)						
Model 1	-0.88	<0.001	-0.90	<0.001	0.64	0.004
Model 2	-0.81	0.001	-0.82	<0.001	0.73	0.002
Model 3	n/a		-0.68	0.004	0.58	0.014

Sleep duration variability is defined as the within-person standard deviation of sleep duration and is measured in minutes
Model 1 adjusted for age, sex, race, and field center
Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education
Model 3 adjusted for model 2, plus sleep duration

Supplementary Table 3.2: Adjusted means of adiposity measures by categories of sleep duration, efficiency and variability restricted to those without sleep apnea (AHI<15): The Multi-Ethnic Study of Atherosclerosis 2011-2013

Sleep Duration	<5 hours	5-6 hours	6-7 hours	7-8 hours	>8 hours	P for trend
N	135	241	427	354 (Referent)	143	
BMI						
Model 1	28.4*	28.3 **	27.7	27.2	27.7	0.009
Model 2	28.3*	28.4**	27.8	27.2	27.8	0.028
Waist Circumference						
Model 1	98.2*	98.2*	96.9	95.4	97.2	0.058
Model 2	97.6	98.2*	97.1	95.5	97.8	0.214
Total Body Fat						
Model 1	24.5	24.7*	23.8	22.9	23.6	0.049
Model 2	24.3	24.8*	23.9	23.0	23.9	0.128

Sleep Efficiency	<85%	85-87.9%	87.9-90.4%	90.4-92.4%	>92.4%	
N	105	175	321	341	358 (Referent)	
BMI						
Model 1	27.5	29.0***	27.9	27.6	27.3	0.010
Model 2	27.4	29.1***	28.0	27.5	27.4	0.018
Model 3	27.2	29.1***	28.0	27.6	27.4	0.043

Waist Circumference						
Model 1	96.8	100.1***	97.3	96.6	95.3	0.003
Model 2	96.1	100.3***	97.5	96.6	95.5	0.015
Model 3	95.9	100.3***	97.5	96.6	95.6	0.021
Total Body Fat						
Model 1	23.8	25.9***	24.0	23.5	22.8	0.005
Model 2	23.4	26.1***	24.2	23.4	23.0	0.014
Model 3	23.2	26.1**	24.2	23.4	23.0	0.026
Sleep	<=48	48-70	70-99	99-262		
Duration	335	348	301	316		
Variability	(Referent)					
N						
BMI						
Model 1	27.5	27.8	27.8	28.0		0.245
Model 2	27.6	27.8	27.8	28.1		0.272
Model 3	27.7	27.9	27.7	27.9		0.670
Waist Circumference						
Model 1	95.8	97.1	97.2	97.6		0.090
Model 2	96.0	97.1	97.0	97.9		0.110
Model 3	96.2	97.2	97.0	97.7		0.239
Total Body Fat						
Model 1	23.2	23.7	23.9	24.3		0.124
Model 2	23.3	23.8	23.8	24.5		0.139

Model 3	23.5	23.9	23.8	24.4	0.306

Sleep duration variability is defined as the within-person standard deviation of sleep duration and is measured in minutes

*p<0.05, **p<0.01, ***p<0.001

Model 1 adjusted for age, sex, race, and field center

Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education

Model 3 adjusted for model 2, plus sleep duration

Supplemental Table 3.3: Sleep efficiency and adiposity stratified by sex: The Multi-Ethnic Study of Atherosclerosis

BMI	<85%	85-87.9%	87.9-90.4%	90.4%-92.4%	>92.4%	P for interaction
Model 1						0.0074
Men	28.7 (28.0, 29.5)	28.5 (27.9, 29.1)	28.2 (27.6, 28.7)	28.5 (28.0, 29.1)	28.2 (27.6, 28.7)	
Women	30.0* (28.7, 31.3)	30.5*** (29.6, 31.5)	29.4* (28.7, 30.0)	28.9 (28.3, 29.6)	28.3 (27.7, 28.9)	
Model 2						0.0050
Men	28.5 (27.7, 29.3)	28.6 (27.9, 29.2)	28.3 (27.7, 28.9)	28.6 (28.0, 29.2)	28.3 (27.7, 28.9)	
Women	30.0* (28.6, 31.3)	30.6*** (29.6, 31.5)	29.6* (28.9, 30.2)	28.8 (28.2, 29.5)	28.4 (27.8, 29.1)	
Waist Circumference						
Model 1						0.0069
Men	103.1 (101.1, 105.2)	101.8 (100.1, 103.6)	100.6 (99.1, 102.1)	102.4 (100.8, 104.0)	101.0 (99.4, 102.6)	
Women	100.0* (96.6, 103.4)	101.5*** (99.1, 103.9)	98.6** (96.9, 100.3)	97.8* (96.1, 99.5)	95.4 (93.7, 97.0)	
Model 2						0.0058
Men	102.4 (100.2, 104.5)	102.0 (100.2, 103.9)	101.0 (99.4, 102.6)	102.4 (100.7, 104.1)	101.2 (99.5, 102.8)	

Women	100.1*	101.6***	98.8*	97.7	95.6	
	(96.5, 103.6)	(99.1, 104.2)	(97.1, 100.5)	(95.9, 99.4)	(93.9, 97.4)	
Total Body Fat						
Model 1						0.0490
Men	22.5	22.0	21.0	21.9	20.8	
	(21.0, 24.1)	(20.7, 23.3)	(19.8, 22.1)	(20.7, 23.1)	(19.6, 22.0)	
Women	29.3	30.6***	29.1**	28.1	26.5	
	(26.8, 31.7)	(28.9, 32.3)	(27.9, 30.3)	(26.9, 29.3)	(25.4, 27.7)	
Model 2						0.0467
Men	22.1	22.0	21.1	22.0	20.9	
	(20.4, 23.8)	(20.7, 23.4)	(19.9, 22.4)	(20.7, 23.3)	(19.6, 22.2)	
Women	29.2	30.5**	29.3**	27.9	26.9	
	(26.7, 31.8)	(28.7, 32.3)	(28.1, 30.6)	(26.7, 29.1)	(25.7, 28.1)	

p<0.05, **p<0.01, ***p<0.001
Model 1 adjusted for age, sex, race, and field center
Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education

Supplemental Table 3.4: Sleep efficiency and waist circumference stratified by age: The Multi-Ethnic Study of Atherosclerosis

	<85%	85-87.9%	87.9-90.4%	90.4%-92.4%	>92.4%	P for Interaction
Model 1						0.0349
Age <=68	102.5***	102.3***	99.4*	99.9**	96.6	
	(99.7, 105.3)	(100.3, 104.4)	(97.8, 101.0)	(98.2, 101.6)	(94.9, 98.3)	
Age > 68	100.2	100.2	99.9	99.7	99.2	
	(97.7, 102.7)	(98.0, 102.4)	(98.2, 101.5)	(98.0, 101.3)	(97.6, 100.7)	
Model 2						0.1274
Age <=68	102.2**	102.5***	99.7*	99.7*	96.9	
	(99.3, 105.1)	(100.3, 104.6)	(98.1, 101.4)	(98.0, 101.4)	(95.1, 98.7)	
Age > 68	99.7	100.4	99.9	99.9	99.3	
	(97.1, 102.3)	(98.0, 102.8)	(98.2, 101.6)	(98.2, 101.6)	(97.6, 100.9)	

p<0.05, **p<0.01, ***p<0.001
Model 1 adjusted for age, sex, race, and field center
Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education

Supplemental Table 3.5: Sleep duration and adiposity stratified by sex: The Multi-Ethnic Study of Atherosclerosis

BMI	<5 hours	5-6 hours	6-7 hours	7-8 hours	>8 hours	P for interaction
Model 1						0.0612
Men	29.6***	28.3	28.4	27.6	27.9	
	(29.0, 30.3)	(27.7, 28.9)	(27.9, 28.9)	(27.1, 28.2)	(26.9, 28.8)	
Women	30.5**	30.2**	28.8	28.7	28.5	
	(29.4, 31.6)	(29.4, 31.0)	(28.2, 29.4)	(28.1, 29.3)	(27.6, 29.4)	
Model 2						0.0462
Men	29.6***	28.5	28.4	27.7	28.0	
	(28.9, 30.3)	(27.8, 29.1)	(27.9, 28.9)	(27.1, 28.3)	(27.0, 29.0)	
Women	30.7**	30.4**	29.0	28.7	28.4	
	(29.5, 31.9)	(29.5, 31.2)	(28.4, 29.6)	(28.0, 29.3)	(27.5, 29.4)	
Waist Circumference	<5 hours	5-6 hours	6-7 hours	7-8 hours	>8 hours	P for interaction
Model 1						0.0885
Men	105.1***	101.2	101.4	99.9	100.7	
	(103.4, 106.9)	(99.5, 102.9)	(100.1, 102.6)	(98.2, 101.5)	(98.2, 103.3)	
Women	100.1*	100.8**	97.5	96.5	97.0	
	(97.1, 103.0)	(98.7, 102.9)	(95.9, 99.1)	(94.9, 98.1)	(94.6, 99.4)	
Model 2						0.0988
Men	104.8***	101.5	101.4	100.0	101.2	
	(102.9, 106.7)	(99.7, 103.3)	(100.1, 102.8)	(98.3, 101.7)	(98.4, 103.9)	
Women	100.1*	101.0**	98.0	96.4	96.9	
	(97.1, 103.2)	(98.8, 103.2)	(96.4, 99.7)	(94.7, 98.0)	(94.4, 99.4)	

p<0.05, **p<0.01, ***p<0.001

Model 1 adjusted for age, sex, race, and field center
Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education

Supplementary Table 3.6: Prevalence of obesity by sleep exposure: The Multi-Ethnic Study of Atherosclerosis

Sleep Duration	<5 hours	5-6 hours	6-7 hours	7-8 hours (Referent)	>8 hours
N	288	388	679	559	241
Overweight					
Model 1	0.07	0.09*	0.00	Ref.	-0.04
Model 2	0.07	0.09*	0.01	Ref.	-0.02
Model 3	0.03	0.07	0.01	Ref.	-0.04
Obese					
Model 1	0.16***	0.12**	0.04	Ref.	-0.02
Model 2	0.16***	0.14***	0.05	Ref.	0.00
Model 3	0.08	0.11**	0.04	Ref.	0.00
Waist circumference					
Model 1	0.10**	0.05	0.01	Ref.	0.01
Model 2	0.09**	0.05	0.02	Ref.	0.01
Model 3	0.05	0.04	0.02	Ref.	0.01
Sleep Efficiency	<85%	85-87.9%	87.9-90.4%	90.4-92.4%	>92.4% (Referent)
N	208	329	544	523	547
Overweight					
Model 1	0.06	0.07	0.02	-0.03	Ref.
Model 2	0.06	0.04	0.03	-0.04	Ref.
Model 3	0.05	0.03	0.02	-0.04	Ref.
Obese					
Model 1	0.10*	0.12**	0.09**	0.02	Ref.
Model 2	0.09	0.10*	0.09**	0.01	Ref.
Model 3	0.04	0.05	0.07*	0.02	Ref.
Waist Circumference					

Model 1	0.06	0.09**	0.07*	0.02	Ref.
Model 2	0.04	0.10**	0.07*	0.03	Ref.
Model 3	0.01	0.07*	0.06*	0.04	Ref.
Sleep duration Variability	<=48 (Referent)	48-70	70-99	99-262	
N	535	554	523	539	
Overweight					
Model 1	Ref.	0.04	0.00	0.01	
Model 2	Ref.	0.02	-0.02	0.01	
Model 3	Ref.	0.04	0.00	0.02	
Obese					
Model 1	Ref.	-0.01	0.04	0.05	
Model 2	Ref.	-0.01	0.03	0.05	
Model 3	Ref.	-0.04	-0.01	0.00	
Waist circumference					
Model 1	Ref.	0.03	0.06	0.06*	
Model 2	Ref.	0.02	0.05	0.06*	
Model 3	Ref.	0.02	0.04	0.04	

Reference is normal weight (BMI<25)
*p<0.05, **p<0.01, ***p<0.001
Sleep duration variability is defined as the within-person standard deviation of sleep duration and is measured in minutes
Model 1 adjusted for age, sex, race, and field center
Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education
Model 3 adjusted for model 2, plus sleep apnea

Supplementary Table 3.7: Prevalence of obesity by sleep exposure among those with AHI<15: The Multi-Ethnic Study of Atherosclerosis

Sleep Duration	<5 hours	5-6 hours	6-7 hours	7-8 hours	>8 hours
N	135	241	427	354 (Referent)	143
Overweight					
Model 1	0.02	0.08	0.03	Ref.	-0.04
Model 2	0.00	0.07	0.03	Ref.	-0.04
Obese					
Model 1	0.15*	0.14**	0.07	Ref.	0.06
Model 2	0.15*	0.17**	0.08*	Ref.	0.09
Waist circumference					
Model 1	0.06	0.07	0.03	Ref.	0.08
Model 2	0.05	0.06	0.04	Ref.	0.08
Sleep Efficiency	<85%	85-87.9%	87.9-90.4%	90.4-92.4%	>92.4%
N	105	175	321	341	358 (Referent)
Overweight					
Model 1	0.05	0.07	0.09*	-0.04	Ref.
Model 2	0.06	0.07	0.08	-0.05	Ref.
Obese					
Model 1	0.04	0.13*	0.09*	0.00	Ref.
Model 2	0.04	0.12*	0.09*	-0.01	Ref.
Waist Circumference					
Model 1	-0.01	0.12**	0.08*	0.01	Ref.
Model 2	-0.04	0.13**	0.08*	0.02	Ref.
Sleep Duration Variability	<=48	48-70	70-99	99-262	
N	335 (Referent)	348	301	316	
Overweight					
Model 1	Ref.	0.08	0.01	0.01	
Model 2	Ref.	0.06	0.00	0.02	
Obese					

Model 1	Ref.	-0.01	0.00	0.02
Model 2	Ref.	-0.02	-0.01	0.01
Waist circumference				
Model 1	Ref.	0.05	0.06	0.08*
Model 2	Ref.	0.04	0.05	0.08*

Reference is normal weight (BMI<25)
*p<0.05, **p<0.01, ***p<0.001
Sleep duration variability is defined as the within-person standard deviation of sleep duration and is measured in minutes
Model 1 adjusted for age, sex, race, and field center
Model 2 adjusted for model 1, plus depressive symptoms, anti-depressants, alcohol use, sleep medication, smoking, income, marital status, and education

Chapter 4: Manuscript 3 - Joint effects of OSA and self-reported sleepiness on incident CHD and stroke

Abstract

Background: Although daytime sleepiness is a common symptom of obstructive sleep apnea (OSA), and both daytime sleepiness and OSA have separately been associated with increased risk of cardiovascular disease (CVD), their joint association with CVD risk is unknown. Consideration of both OSA and daytime sleepiness may help refine the OSA phenotype.

Methods: Among 3,504 Sleep Heart Health Study participants, OSA was assessed by at-home polysomnography and daytime sleepiness by the Epworth Sleepiness Scale. Outcomes included total CVD events (coronary heart disease (CHD) and stroke), as well as CHD and stroke separately. Cox proportional hazard regression was used.

Results: Over a median of 11.5 years of follow-up, 627 cohort participants developed incident CVD, 533 incident cases of CHD and 181 incident cases of stroke. Compared to those without OSA (apnea hypopnea index (AHI) <5) and without adjustment for daytime sleepiness, the hazard ratios (95% CI) for the association of moderate-severe OSA (AHI ≥15) were for CVD 1.20 (0.97-1.49), for CHD 1.22 (0.97-1.53), and for stroke 1.30 (0.87-1.93). There also were weak associations between daytime sleepiness (yes vs. no) and risk of CVD [1.19 (0.99-1.43)] and CHD [1.22 (1.01-1.49)], and none for

stroke [0.99 (0.69-1.42)]. When modeled jointly, having both AHI ≥15 and daytime sleepiness (compared with having AHI <5 and no sleepiness) was associated with HRs of 1.34 (0.96-1.87) for CVD, 1.41 (0.99-2.00) for CHD and 1.30 (0.69-2.47) for stroke. For all outcomes, there were no statistically significant interactions between daytime sleepiness and OSA on the multiplicative or additive scales.

Conclusions: These findings suggest that routine assessment of daytime sleepiness, in addition to OSA, may not provide additional information about sleep related risk of developing CVD.

Background

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing characterized by the repetitive partial or total collapse of the upper airway during sleep. In severe cases, patients suffer from hypoxia, arousal and sleep fragmentation, which may lead to reduced cognitive function and lower quality of life.[48] OSA is highly prevalent among older adults; recent data from the Multi-Ethnic Study of Atherosclerosis suggests 15% have severe OSA, defined as an apnea-hypopnea index (AHI) $\geq$ 30.[13] Although daytime sleepiness is the most common symptom of OSA,[275] neither the relationship between OSA and daytime sleepiness, nor the impact of presenting with both OSA and daytime sleepiness, is well understood. Daytime sleepiness is higher among individuals with more severe OSA,[276] but the majority of people with OSA do not report daytime sleepiness.[49] In prior work from the community-based Sleep Hearth Health Study (SHHS), greater non-rapid eye movement (REM) but not greater REM sleep disordered breathing was associated with excessive daytime sleepiness.[277] Daytime sleepiness may be more common among individuals who attend sleep clinics to be screened for OSA, because the sleepiness symptoms may be prompting them to seek formal OSA evaluation.

Both OSA and daytime sleepiness have been associated with adverse health outcomes. OSA has been associated positively with cardiovascular risk factors and outcomes, including diabetes,[170] hypertension,[167,173] coronary heart disease,[174] stroke,[175] heart failure,[174] atrial fibrillation,[179] and mortality,[176,178] though some studies are limited by measurement error and/or selection bias. Although studied less frequently, daytime

sleepiness has also been associated with increased incident cardiovascular morbidity and mortality.[278,279] Few studies have explored the joint associations or interactions between OSA and daytime sleepiness in relation to risk of cardiovascular disease (CVD). In prior research, those with both snoring, a surrogate of OSA, and daytime sleepiness had a significantly increased rates of incident CVD[280] and mortality[281], compared to those who had neither. It is possible that having both OSA and daytime sleepiness may be a marker of more severe OSA, and thus possibly greater CVD risk. However, it is presently unknown whether OSA and daytime sleepiness are independent risk factor for CVD incidence or whether there is a statistical or biological interaction between OSA and daytime sleepiness in relation to CVD incidence.

Examining the interrelation of OSA and daytime sleepiness with CVD risk may help refine the OSA phenotype, and possibly result in stronger associations with risk of CVD events than when either OSA or daytime sleepiness is evaluated alone. Therefore, the objectives of this study were to, among participants of the community-based SHHS study, determine the joint association of habitual daytime sleepiness and OSA with risk of CVD events, and to evaluate whether statistical or biological interaction is present between OSA and daytime sleepiness in relation to CVD.

Methods

The SHHS is a longitudinal study designed to determine whether sleep disordered breathing is an independent risk factor for CVD. At its inception, it included participants from six different already existing cohort studies: the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham

Heart Study, the Strong Heart Study, the New York Hypertension Cohort, the Tucson Epidemiologic Study of Airways Obstructive Diseases, and the Health and Environment Study. Participants invited to take part in SHHS were at least 40 years of age, had no CPAP, oral device treatment, oxygen therapy, or tracheostomy. Young snorers were oversampled. A total of 6,441 participants were recruited for the baseline examination in 1995-1998.

Our analytic sample excluded all participants from the New York site (n = 760) due to data quality issues, those missing data on exposures (n = 222 for ESS, n = 703 for AHI), those who reported CPAP use (n = 7), and those missing or without follow-up time (n = 17). We also excluded, from relevant analyses, participants with prevalent myocardial infarction (n = 240), revascularization (n=125) or stroke (n = 117) as defined by the parent cohorts, as well as those missing data on myocardial infarction, revascularization, CHD death, and stroke (n = 411). This left a final analytic sample of 3,504 participants for the combined CVD analysis, 3,599 participants for the CHD analysis and 3,791 participants for the stroke analysis.

Sleep variables

The Epworth Sleepiness Scale (ESS) was used to measure daytime sleepiness.[282] This eight-item questionnaire asks about the likelihood of falling asleep on a scale from 0-3. These items are then summed, with scores ≥11 representing abnormal sleepiness. SHHS used a modified version of the scale that performed similarly to the original version.[283] For analysis, daytime sleepiness was represented dichotomously.

At-home polysomnography was performed with the Compumedics P Series System (Abbotsford, Victoria, Australia). All sensors were placed and equipment calibrated during the home visit. Channels were recorded as follows: electroencephalogram, chin electromyogram, thoracic and abdominal displacement, airflow, finger pulse oximeter, a single bipolar electrocardiogram, body position by an Hg gauge sensor, and ambient light level. Data were stored in real time, reviewed locally, and forwarded to the central reading center at Case Western Reserve University (Cleveland, OH). Apneas were defined as the absence or near absence of airflow (<25% of baseline) for at least ten seconds. Hypopneas were defined as below 70% of the baseline amplitude for at least ten seconds.[283] For defining both apneas and hypopneas, also required was 4% or higher oxyhemoglobin desaturation. AHI was calculated as the average number of apneas and hypopneas per hours of sleep and was modeled categorically (<5, 5-14.9, ≥15).

Outcome ascertainment

All incident CVD events were defined as the first occurrence between baseline (the date of overnight polysomnography) and the end of follow-up, which ranged from 2008-2011 depending on the parent cohort. Event definitions were similar to those used in previous SHHS analyses.[174,175] Within SHHS, event surveillance occurred according to individual cohort protocols, which included participant phone calls and mailings as well as surveillance of death certificates and hospital discharge records. Physicians classified events according to cohort specific protocols.[284-290]

For the present analysis, three separate CVD endpoints were considered. Incident CHD was defined as first myocardial infarction (MI), CHD death, or coronary revascularization. MI occurrence was classified similarly across the cohorts, and was based on symptoms of cardiac pain, electrocardiograms suggesting ischemia, and/or elevated cardiac biomarker patterns.[283] Incident stroke was defined as the first fatal or nonfatal ischemic stroke. Stroke classification used computed tomography and magnetic resonance images when available. Incident CVD included all CHD and stroke events as defined above.

Covariates

Demographic data, including information on age, sex, race/ethnicity, and education, were self-reported. Weight and height were measured at the baseline SHHS visit using a standardized protocol. Body mass index (BMI) was calculated in kg/m^2. Smoking status was categorized as current, former, or never smoker. Habitual alcohol intake was measured in drinks per week in the parent cohorts.

Analysis

Descriptive statistics were calculated for exposure variables at baseline. Cox proportional hazards models were used to model time to each CVD event relative to baseline. Person-time was calculated from the baseline examination until an event, loss to follow-up, death, or the end of the follow-up period for each cohort. The proportional hazards assumption was checked using interactions with time and tests of correlations of the residuals, and no meaningful violations were found. The main associations of daytime sleepiness and OSA, separately, on CVD, CHD, and stroke are presented, as well

as the joint associations. We then evaluated independence of the associations in the main models by controlling jointly for OSA categories and daytime sleepiness in a proportional hazards (multiplicative) model. Interactions were also tested on both the additive scale using the relative excessive risk due to interaction (RERI) and on the multiplicative scale using cross-product terms and presented in accordance with published recommendations.[291] To further demonstrate the joint associations, we presented hazard ratios (HRs) with confidence intervals (CIs) and p-values for each stratum of daytime sleepiness and OSA with one reference category, as well as the association of OSA with the outcomes within strata of daytime sleepiness and the association of daytime sleepiness on the outcomes within strata of OSA. For the joint models, categorization of the exposures were as follows: AHI <15 & ESS < 11, AHI ≥ 15 & ESS < 11, AHI < 15 & ESS ≥ 11, and AHI ≥ 15 & ESS ≥ 11. Effect modification by sex was also examined, and sex-stratified results are reported in supplemental material.

Potential confounders included age, race, sex, education, alcohol, smoking status, and BMI. Diabetes, dyslipidemia, and hypertension are likely to lie on the causal pathway between sleep disorders and CVD and were thus not included in the models. SAS version 9.3 (SAS Institute, Cary, NC) was used to analyze the data.

Results

The mean age at baseline was 63.8 years and 55.5% of the sample was female. Mean AHI at baseline was 9.4 events/hour; 19.2% had an AHI value ≥15 indicating moderate or severe OSA, and 6.5% had an AHI ≥30, indicating severe OSA. The mean ESS score was 7.6, and 23.3% had values >11, indicating daytime sleepiness. OSA and

daytime sleepiness were somewhat correlated: among those with AHI < 5, mean ESS score was 7.3, while mean ESS score for those with AHI ≥15 was 8.3. Among those with no daytime sleepiness, mean AHI was 8.8 events/hour, while mean AHI was 11.5 among those with daytime sleepiness. AHI also increased with BMI category; while normal weight adults had an AHI of 5.8 ± 10.3, while mean AHI for overweight was 8.0 ± 10.0 and 14.2 ± 16.1 for obese.

Table 4.1 shows sociodemographic and behavioral characteristics by AHI category. Those with AHI ≥ 15 were more likely to be male, older, and have a higher BMI, and have daytime sleepiness than those with AHI < 15.

Over a median of 11.5 years of follow-up, we identified 627 incident cases of CVD, 533 incident cases of CHD, and 181 incident cases of stroke. The crude incidence rate per 1000 person-years was 17.6 (95% CI: 16.2-19.0) for CVD, 14.4 (13.2-15.7) for CHD and 4.5 (3.9-5.2) for stroke.

Table 4.2 shows adjusted HRs and 95% CIs of the association between OSA and incident CVD, CHD and stroke, without considering daytime sleepiness. After adjustment for demographics and compared to no OSA (AHI <5), the HRs (95% CIs) for moderate/severe OSA (AHI ≥15) and risks of CVD, CHD, and stroke were 1.20 (0.97-1.49), 1.22 (0.97-1.53) and 1.30 (0.87-1.93), respectively. Overall, compared to no OSA (AHI < 5), the magnitudes of the associations for mild OSA (AHI 5-<15) were slightly larger than for moderate or severe OSA (AHI ≥ 15); however, they were only statistically significant for CVD ($HR_{\text{mild vs no OSA}}$: 1.27 (1.05-1.53)) and CHD ($HR_{\text{mild vs no OSA}}$: 1.27 (1.03-1.56)), but not for stroke ($HR_{\text{mild vs no OSA}}$: 1.37 (0.97, 1.94)). Most associations were

attenuated after adjustment for alcohol, smoking, and BMI in Model 2. When stratified by sex, the OSA-stroke associations were larger for men than for women, though the sex interaction was not statistically significant (p = 0.18, **Supplemental Table 4.1**).

Adjusted HRs and 95% CIs of the association of daytime sleepiness with incident CVD, CHD, and stroke can be found in **Table 4.3**. After adjustment for demographics, there were modest associations between daytime sleepiness (yes vs. no) and risk of CVD (HR: 1.19 (0.99-1.43)) as well as CHD (HR: 1.22 (1.01-1.49)). There was significant effect modification by sex for daytime sleepiness and stroke, whereby men were at higher risk of stroke with daytime sleepiness (HR: 1.36 (0.84-2.20)), whereas women were at lower risk (HR: 0.67 (0.38-1.21)), though confidence intervals were wide (**Supplemental Table 4.2**). Results were similar after adjustment for alcohol, smoking, and BMI.

Figure 4.1 shows the crude incidence rates for incident CVD by daytime sleepiness and OSA status jointly. Although those with mild and moderate-severe OSA had much higher incidence rates than those with no OSA, those with daytime sleepiness had only slightly higher CVD incidence rates across OSA categories. This is consistent with Table 4.2 Model 3, where the hazard ratio for OSA was altered little by adjustment for daytime sleepiness.

Supplemental Tables 4.3-4.5 show in more detail adjusted hazard ratios and 95% confidence intervals for the joint associations of OSA and daytime sleepiness with CVD, CHD, and stroke. On both the additive and multiplicative scales, there were no statistically significant interactions between OSA and daytime sleepiness for any outcomes. Compared to those without daytime sleepiness and less than moderate OSA

(AHI <15), those with daytime sleepiness and at least moderate OSA (AHI ≥ 15) had a slightly higher risk of incident CVD (HR: 1.34 (0.96-1.87)), CHD (HR: 1.41 (0.99-2.00)), and stroke (HR: 1.30 (0.69-2.47)) that did not reach statistical significance.

Discussion

In this prospective community-based cohort, we present some of the first information on the joint association of daytime sleepiness and polysomnography-measured OSA with risk of incident CVD. In a multiplicative proportional hazards model, daytime sleepiness added little beyond OSA as a risk factor for CVD, and similarly there was no statistically significant interaction between daytime sleepiness and OSA with any of the CVD outcomes. The associations with CVD for both OSA and daytime sleepiness were rather modest, and our study was not big enough to rule out a small independent or synergistic association for daytime sleepiness. Specifically, after adjustment for potential confounding CVD risk factors, there were modest (but not statistically significant) associations between OSA and all outcomes, while for daytime sleepiness, there were weak positive associations with CVD and CHD, but none for stroke.

As mentioned, we found no statistically significant interaction between polysomnography-measured OSA and daytime sleepiness with incident CVD, CHD, and stroke. Previous research evaluating the interrelationship between OSA and daytime sleepiness on CVD used snoring as a surrogate for OSA and did not examine statistical interaction.[280,281,291] In one study of older adults, those reporting both snoring and sleepiness were significantly more likely to develop an incident CVD event compared to

those reporting no snoring or sleepiness, while there was no association when either snoring or sleepiness occurred in isolation.[280] Another study of middle-aged men found a nearly two-fold HR of overall mortality for the combination of snoring and daytime sleepiness (versus having neither), but a smaller non-significant association with CVD mortality (HR=1.2).[281] Both joint associations were associated with a nearly three-fold higher risk of overall and CVD-specific mortality for those under the age of sixty, but were null among those over age sixty.

Counter to expectation, the associations between OSA and incident CHD and stroke did not display a dose-response and were statistically significant only for mild OSA, though the results were independent of daytime sleepiness. It is possible that more serious OSA was treated after baseline, since treatment later during the follow-up period was not captured in the dataset. Treatment may have lowered CVD risk among those with higher AHI while those with lower AHI remained untreated. In meta-analyses, OSA has been associated with greater risk of CVD,[181,292] with associations stronger and more consistent for stroke than CHD. However, many of these studies contain threats to validity, including non-objective measurement of OSA, clinic-based samples, and short follow-up. Few community-based studies exist that used polysomnography-measured OSA in association with incident CHD and stroke.[174,175,293] Published SHHS data only showed positive associations between OSA and CHD among men with AHI $\geq$ 30, but there was no association among women or men with mild or moderate OSA. For stroke, OSA was associated with a two to three-fold higher risk in men but not women, similar to what we found in the main effects analyses. In the younger Wisconsin Sleep Cohort

consisting of both men and women, severe OSA was associated with nearly 2.5 times greater risk of incident CHD, [293] suggesting that the association may be stronger and more consistent among middle-aged adults.

In main effect analyses we also found daytime sleepiness to be associated with slightly greater risk of incident CVD and CHD, independent of OSA. When both sexes were included, there was no association between daytime sleepiness and risk of incident stroke, however in stratified analyses men with daytime sleepiness had a higher risk of incident stroke, but women did not. Several community-based cohorts have found significant positive associations between daytime sleepiness and CVD events, including CHD and stroke,[278,294-296] with a variety of different measures of daytime sleepiness.

One limitation of this analysis is that the Sleep Heart Health Study participants had a relatively low prevalence of both OSA and daytime sleepiness, resulting in small cells in the joint category (5% of sample). This limited precision and thus statistical power to detect as statistically significant the weak associations observed. However, given our findings, large associations are unlikely. In addition, the low prevalence of OSA in this sample made it necessary to categorize OSA using the combination of moderate and severe OSA (AHI $\geq$15), so we are unable to provide information about the joint association of severe OSA (AHI $\geq$30) and daytime sleepiness with CVD risk. Other study limitations include only one night of polysomnography, so the obtained data may not be indicative of habitual sleep patterns due to the "first-night effect", where sleep architecture and efficiency are altered as a result of measurement.[297] Additionally, those with OSA may have obtained treatment, and if protective, it could have depressed the

magnitude of the associations. We removed those reporting treatment at baseline, but we lacked information on those who started treatment during follow-up. Despite these weaknesses, the study also has several strengths, which include OSA assessed via polysomongraphy, a longitudinal design, and physician review and classification of CVD events.

OSA is a common condition associated with moderately greater risk of CVD events and risk factors in many observational studies, and experimental studies in both human and animal models suggest a pathophysiological role.[181] Although symptoms of daytime sleepiness can prompt patients to go to the doctor for diagnosis, the majority of those with OSA do not have daytime sleepiness.[49] Because daytime sleepiness is easy to assess and represents habitual sleepiness, it could be useful as a clinical screening tool for identifying OSA. If a strong interaction between daytime sleepiness and OSA were found for risk of developing CVD, and causality could be established, it could suggest that it may be useful to add daytime sleepiness to OSA screening with an aim to reduce CVD events, though further research on the effectiveness of OSA screening is necessary. However, in the present study there was no statistically significant interaction between daytime sleepiness and OSA on CVD risk and the joint associations suggested that collecting information on daytime sleepiness adds little beyond OSA in relation to incidence of CVD.

Table 4.1: Participant characteristics by Apnea-Hypopnea Index (AHI) category: The Sleep Heart Health Study

	AHI <5	AHI ≥ 5 & < 15	AHI ≥ 15
N total	1772	1058	674
Demographics			
Age, mean years ± SD	61.9 ± 10.5	65.2 ± 10.3	66.7 ± 9.7
% Female, n (%)	1182 (66.7)	508 (48.0)	253 (37.5)
Race, n (%)*			
White	1508 (49.9)	915 (30.3)	601 (17.2)
Black	133 (52.2)	70 (27.5)	52 (20.4)
Other	131 (58.2)	73 (32.4)	21 (9.3)
Ethnicity, n (%)*			
Hispanic/Latino	97 (57.4)	55 (32.5)	17 (10.1)
Not Hispanic/Latino	1675 (50.2)	1003 (30.1)	657 (19.7)
Education, n (%)*			
Less than high school	113 (39.8)	106 (37.3)	65 (22.9)
High School	862 (49.5)	536 (30.8)	343 (19.7)
College	529 (52.9)	276 (27.6)	195 (19.5)
Post-college	66 (42.6)	57 (36.8)	32 (20.7)
Behavioral Characteristics			
Daytime Sleepiness, n (%)	365 (20.6)	263 (24.9)	189 (28.0)
Smoking status, n (%) *			
Current Smoker	211 (63.9)	75 (22.7)	44 (13.3)
Former Smoker	700 (46.0)	508 (33.4)	313 (20.6)
Never Smoker	855 (52.1)	472 (28.8)	314 (19.1)
Body mass index, mean ± SD	27.1 ± 4.5	29.0 ± 4.8	30.8 ± 5.6
Alcohol use, drinks per day	2.2 ± 4.6	2.9 ± 5.9	2.9 ± 6.7

* Row percentages

Table 4.2: Adjusted hazard ratios (95% confidence interval) of sleep apnea with risk of incident cardiovascular disease, overall and by sex: The Sleep Heart Health Study

OSA category	Normal (AHI <5)	Mild (AHI ≥5 to <15)	Moderate/Severe (AHI ≥15)
CVD			
N event	237	234	156
N total	1772	1058	674
Model 1	Ref.	1.27* (1.05, 1.53)	1.20 (0.97, 1.49)
Model 2	Ref.	1.20 (0.98, 1.46)	1.10 (0.87, 1.38)
Model 3	Ref.	1.19 (0.98, 1.46)	1.09 (0.87, 1.37)
CHD			
N event	200	200	133
N total	1814	1092	693
Model 1	Ref.	1.27* (1.03, 1.56)	1.22 (0.97, 1.53)
Model 2	Ref.	1.18 (0.95, 1.47)	1.11 (0.86, 1.43)
Model 3	Ref.	1.17 (0.94, 1.45)	1.11 (0.87, 1.42)
Stroke			
N event	63	72	46
N total	1873	1156	762
Model 1	Ref.	1.37 (0.97, 1.94)	1.30 (0.87, 1.93)
Model 2	Ref.	1.46* (1.01, 2.10)	1.25 (0.82, 1.93)
Model 3	Ref.	1.46* (1.01, 2.10)	1.25 (0.82, 1.93)

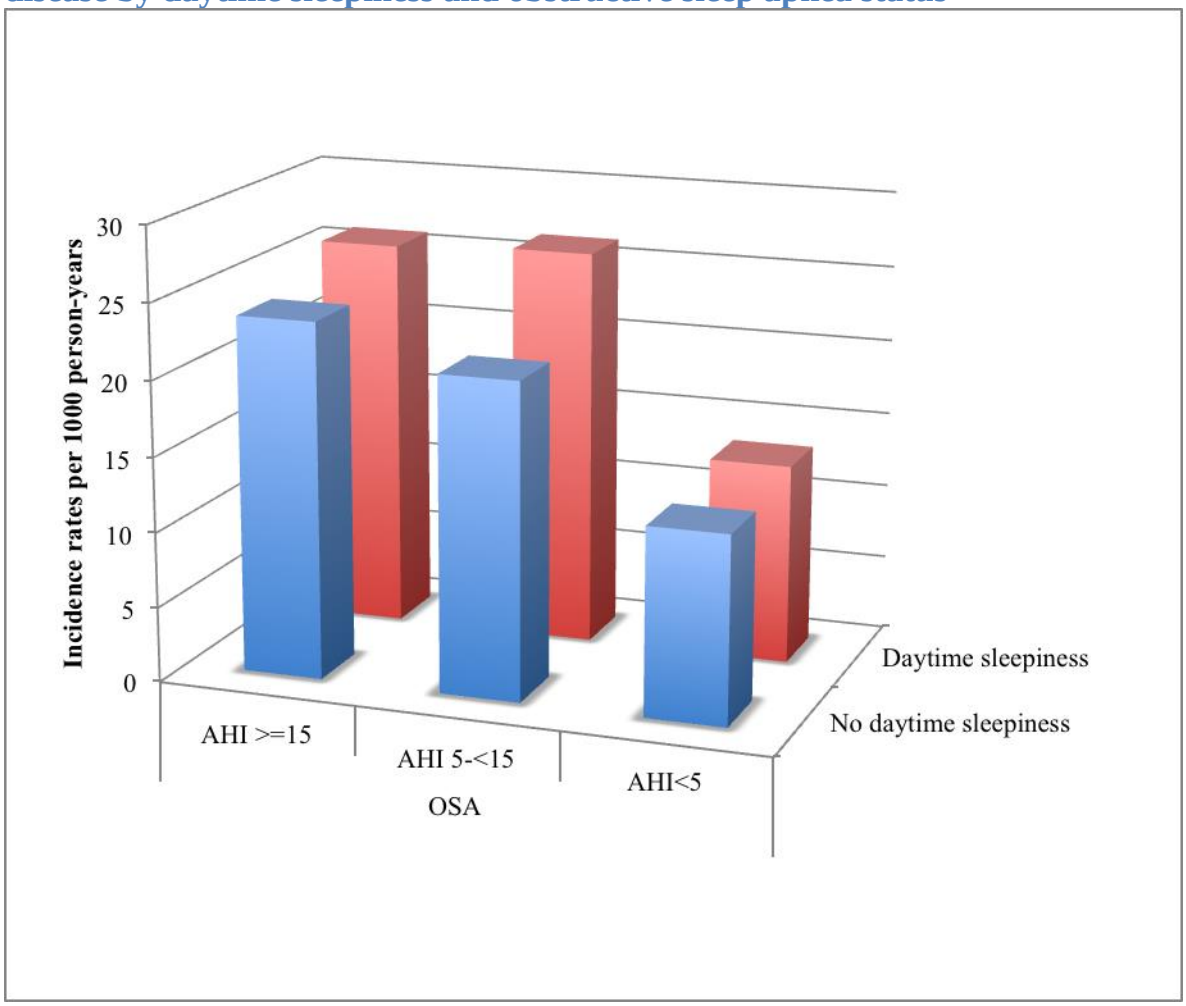
* $p < 0.05$
Model 1 adjusted for age, race, sex, ethnicity, and education.
Model 2 added alcohol, smoking status, pack-years, and BMI
Model 3 added daytime sleepiness
Abbreviations: OSA – obstructive sleep apnea, AHI – apnea-hypopnea index, CVD – cardiovascular disease, CHD – coronary heart disease

Table 4.3: Adjusted hazard ratios (95% confidence interval) of daytime sleepiness with risk of incident cardiovascular disease: The Sleep Heart Health Study

	ESS < 11	ESS ≥ 11
CVD		
N events	463	164
N total	2687	817
Model 1	Ref.	1.19 (0.99, 1.43)
Model 2	Ref.	1.24* (1.03, 1.50)
CHD		
N events	386	147
N total	2760	839
Model 1	Ref.	1.22* (1.01, 1.49)
Model 2	Ref.	1.27* (1.04, 1.56)
Stroke		
N events	142	39
N total	2890	901
Model 1	Ref.	0.99 (0.69, 1.42)
Model 2	Ref.	1.05 (0.72, 1.52)

* $p < 0.05$
Model 1 adjusted for age, race, sex, ethnicity, and education.
Model 2 added alcohol, smoking status, pack-years, and BMI

Figure 4.1: Crude incidence rates per 1000 person-years for cardiovascular disease by daytime sleepiness and obstructive sleep apnea status



Abbreviations: AHI – apnea-hypopnea index, OSA – obstructive sleep apnea

Supplemental Table 4.1: Adjusted hazard ratios (95% confidence interval) of sleep apnea with risk of incident cardiovascular disease by sex: The Sleep Heart Health Study

OSA category	Normal (AHI <5)	Mild (AHI ≥5 to <15)	Moderate/Severe (AHI ≥15)
CVD			
Men			
Model 1	Ref.	1.38 (1.07, 1.79)	1.32 (1.01, 1.74)
Model 2	Ref.	1.30 (1.00, 1.71)	1.21 (0.90, 1.63)
Women			
Model 1	Ref.	1.10 (0.83, 1.46)	1.03 (0.73, 1.47)
Model 2	Ref.	1.09 (0.81, 1.46)	0.95 (0.65, 1.38)
CHD			
Men			
Model 1	Ref.	1.29 (0.98, 1.68)	1.30 (0.98, 1.72)
Model 2	Ref.	1.19 (0.90, 1.58)	1.22 (0.90, 1.65)
Women			
Model 1	Ref.	1.21 (0.87, 1.67)	1.04 (0.68, 1.58)
Model 2	Ref.	1.07 (0.83, 1.38)	0.85 (0.61, 1.19)
Stroke			
Men			
Model 1	Ref.	2.29 (1.23, 4.26)	1.87 (0.97, 3.60)
Model 2	Ref.	2.53 (1.30, 4.95)	1.74 (0.83, 3.64)
Women			
Model 1	Ref.	1.02 (0.66, 1.58)	1.10 (0.64, 1.87)
Model 2	Ref.	1.05 (0.66, 1.66)	1.06 (0.60, 1.87)

* $p < 0.05$
Model 1 adjusted for age, race, sex, ethnicity, and education.
Model 2 added alcohol, smoking status, pack-years, and body mass index
Model 3 added daytime sleepiness

Abbreviations: ESS – Epworth Sleepiness Scale, CVD – cardiovascular disease, CHD – coronary heart disease, AHI – apnea-hypopnea index

Supplemental Table 4.2: Adjusted hazard ratios (95% confidence interval) of daytime sleepiness with risk of incident cardiovascular disease by sex: The Sleep Heart Health Study

	ESS < 11	ESS ≥ 11
CVD		
Men		
Model 1	Ref.	1.16 (0.92, 1.45)
Model 2	Ref.	1.24 (0.98, 1.57)
Women		
Model 1	Ref.	1.29 (0.95, 1.75)
Model 2	Ref.	1.32 (0.96, 1.82)
CHD		
Men		
Model 1	Ref.	1.15 (0.90, 1.45)
Model 2	Ref.	1.22 (0.96, 1.56)
Women		
Model 1	Ref.	1.41 (1.00, 1.98)
Model 2	Ref.	1.47 (1.03, 2.11)
Stroke		
Men		
Model 1	Ref.	1.36 (0.84, 2.20)
Model 2	Ref.	1.59 (0.97, 2.61)

Women		
Model 1	Ref.	0.67 (0.38, 1.21)
Model 2	Ref.	0.62 (0.33, 1.18)

* $p < 0.05$
Model 1 adjusted for age, race, sex, ethnicity, and education.
Model 2 added alcohol, smoking status, pack-years, and BMI
Abbreviations: ESS – Epworth Sleepiness Scale, CVD – cardiovascular disease, CHD – coronary heart disease

Supplemental Table 4.3: Joint association of daytime sleepiness and sleep apnea with risk of incident cardiovascular disease: The Sleep Heart Health Study

	AHI <15		AHI ≥ 15		HR (95% CI); *P* for AHI ≥ 15 vs AHI < 15 within ESS strata
	N with/ without outcome	HR (95% CI); *P*	N with/ without outcome	HR (95% CI); *P*	
ESS <11	353/1849	*Referent*	110/375	0.94 (0.74-1.20); p = 0.64	0.94 (0.74-1.20); p = 0.64
ESS ≥ 11	118/510	1.20 (0.96-1.49); p = 0.11	46/143	1.34 (0.96-1.87); p = 0.09	1.16 (0.80-1.68); p = 0.44
HR (95% CI); P for ESS ≥ 11 vs ESS < 11 within AHI strata		1.20 (0.96-1.49); p = 0.11		1.39 (0.96-2.02); p = 0.08	

Measure of interaction on additive scale (95% CI); *P RERI = 0.19 (-0.31, 0.69); p = 0.46*
Measure of interaction on multiplicative scale (95% CI); chi-square = 0.59, *p = 0.44*
Hazard ratio is adjusted for age, sex, race, ethnicity, education, alcohol, smoking status, pack-years, and BMI
Abbreviations: ESS – Epworth Sleepiness Scale, AHI – apnea-hypopnea index, HR – hazard ratios, CI – confidence intervals

Supplemental Table 4.4: Joint effect of daytime sleepiness and sleep apnea and risk of incident CHD: The Sleep Heart Health Study

	AHI <15		AHI ≥ 15		HR (95% CI); *P* for AHI ≥ 15 vs AHI < 15 within ESS strata
	N with/ without outcome	HR (95% CI); *P*	N with/ without outcome	HR (95% CI); *P*	
ESS <11	295/1971	*Referent*	91/409	0.97 (0.75-1.26); p = 0.81	0.97 (0.75-1.26); p = 0.81
ESS ≥ 11	105/543	1.24 (0.98-1.57); p = 0.08	42/154	1.41 (0.99, 2.00); p = 0.06	1.16 (0.78-1.72); p = 0.46
HR (95% CI); P for ESS ≥ 11 vs ESS < 11 within AHI strata		1.24 (0.98-1.57); p = 0.08		1.36 (0.91-2.02); p = 0.13	

Measure of interaction on additive scale (95% CI); *P RERI = 0.18 (-0.37, 0.72) p =0.53*
Measure of interaction on multiplicative scale (95% CI); *p = 0.52*
Hazard ratio is adjusted for age, sex, race, ethnicity, education, alcohol, smoking status, pack-years, and BMI
Abbreviations: CHD – coronary heart disease, ESS – Epworth Sleepiness Scale, AHI – apnea-hypopnea index, HR – hazard ratios, CI – confidence intervals

Supplemental Table 4.5: Joint effect of daytime sleepiness and sleep apnea and risk of incident stroke: The Sleep Heart Health Study

	AHI <15		AHI ≥ 15		HR (95% CI); *P* for AHI ≥ 15 vs AHI < 15 within ESS strata
	N with/ without outcome	HR (95% CI); *P*	N with/ without outcome	HR (95% CI); *P*	
ESS <11	108/2238	*Referent*	34/510	0.90 (0.58-1.39); p = 0.64	0.90 (0.58-1.39); p = 0.64
ESS ≥ 11	27/656	0.93 (0.59-1.45); p = 0.74	12/206	1.30 (0.69-2.47); p = 0.42	1.39 (0.66-2.95); p = 0.39
HR (95% CI); P for ESS ≥ 11 vs ESS < 11 within AHI strata		0.93 (0.59-1.45); p = 0.74		1.61 (0.79-3.30); p = 0.19	

Measure of interaction on additive scale (95% CI); *P RERI = 0.55 (-0.39, 1.49); p = 0.25*
Measure of interaction on multiplicative scale (95% CI); *p=0.20*
Hazard ratio is adjusted for age, sex, race, ethnicity, education, alcohol, smoking status, pack-years, and BMI
Abbreviations: ESS – Epworth Sleepiness Scale, AHI – apnea-hypopnea index, HR – hazard ratios, CI – confidence intervals

Chapter 5: Manuscript 4 - Diagnosed OSA/CPAP and Risk of Atherosclerotic Cardiovascular Disease among those with Atrial Fibrillation

Abstract

Background: Atrial fibrillation (AF) and obstructive sleep apnea (OSA) are common conditions that frequently coexist. Both AF and OSA are strongly associated with increased risk of stroke and other cardiovascular diseases. However, little is known about the relationship between OSA and atherosclerotic cardiovascular disease among AF patients.

Methods: We used the Truven Health MarketScan databases to construct a prospective cohort of patients with AF from 2007-2014. AF, OSA, stroke, myocardial infarction, and relevant confounders were defined using ICD-9-CM codes. Those with an OSA diagnosis were matched by age, sex, and enrollment date to those without a diagnosis. Cox proportional hazards models adjusted for pre-defined confounders and high-dimensional propensity scores. Migraines were included as a 'control' outcome.

Results: We matched 90,274 individuals with a diagnosis of OSA to 446,903 without. During a mean follow-up of 16 months, there were 4,725 incident ischemic stroke cases and 6,500 incident myocardial infarction cases. After adjustment, an OSA diagnosis was

strongly (and unexpectedly) associated with reduced risk of incident stroke (hazard ratio (HR) = 0.59, 95% confidence interval (CI) 0.53, 0.66) and myocardial infarction (0.49, [0.45, 0.54]). Similar results were found in sensitivity analyses using different definitions of OSA. No association was observed with migraines (HR = 0.87 [95%CI 0.70, 1.08]).

Conclusions: Counterintuitively, an OSA diagnosis in patients with AF was strongly associated with reduced risk of incident atherosclerotic cardiovascular disease. Potential explanations for these paradoxical results, such as low sensitivity and specificity of ICD-9-CM codes to identify OSA or selection bias, deserve further study.

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. For men and women over 40, the lifetime risk of AF is 1 in 4[298] and the prevalence of AF is expected to reach 12.1 million cases in the United States by the year 2030.[299] Those with AF are at increased risk of stroke and myocardial infarction (MI),[300-302] among other complications. Because of AF's high burden, it is necessary to better understand modifiable factors that are associated with adverse outcomes.

Obstructive sleep apnea (OSA) is also increasing in prevalence,[65] potentially due to the obesity epidemic. In the general population, OSA has also been associated with increased risk of AF[179,303-307] as well as stroke and coronary heart disease,[175,181,308] though limitations include study samples, cross-sectional designs, and OSA measurement. AF patients are at especially elevated risk of atherosclerotic cardiovascular disease (CVD) such as ischemic stroke and MI,[300-302] and it is possible that OSA may further increase the risk. Although OSA has been associated with AF,[179,303,304] and stroke and MI are common outcomes among AF patients,[300-302] the few studies examining the relationship between OSA and atherosclerotic CVD in AF patients have reported mixed results, with one finding a positive association and two finding no association.[309-311] Additional research is needed, as these studies had small sample sizes, short follow up time, and/or did not employ optimal methodology to control for important confounders in administrative data. Identification of an association between OSA and atherosclerotic CVD in AF patients may have implications for screening and treatment, in order to prevent atherosclerotic CVD.

Using a large administrative claims database we examined the longitudinal association between diagnosed OSA and risk of MI and ischemic stroke in a large cohort of patients with non-valvular AF. We hypothesized that those AF patients with diagnosed OSA would have an increased risk of ischemic stroke and MI compared to those without an OSA diagnosis.

Methods

The present analysis utilized commercially available de-identified data from two databases licensed by Truven Health MarketScan. The Commercial Claims and Encounters Database is a commercially available de-identified data source for privately insured healthcare plan enrollees under age 65, while the Medicare Supplemental database consists of adults 65 and older with employer-paid Medicare supplemental insurance. The databases contain individual-level information on enrollment and health insurance claims for inpatient and outpatient services, as well as outpatient pharmacy claims. We used these healthcare claims to conduct a prospective cohort study of patients with AF from January 1st, 2007 to December 31st 2014 among those aged 22-99. Because this secondary data is de-identified and commercially available, the University of Minnesota Institutional Review Board deemed it exempt from review.

Sample Selection and Matching

All participants in the analytic sample had non-valvular AF, which was defined as at least one inpatient or two outpatient claims 7 to 365 days apart using the ICD-9-CM codes 427.3, 427.31, or 427.32. Those with ICD-9-CM codes for valvular AF or procedural codes for valvular repair or replacement were excluded from the sample. The

use of administrative claims data to identify AF was summarized in a systematic review, which found the algorithms had a median positive predictive value of 87% and a median sensitivity of 79%.[312] In order to be included in the present analysis, we also required at least 90 days of continuous enrollment before first AF diagnosis, in order to obtain adequate information on confounding variables. For those participants who discontinued enrollment and then re-enrolled, only the first enrollment period was included in the analysis. Additionally, those with a prevalent stroke, MI, or TIA prior to the start of follow-up (index date) were excluded from the analysis.

Individuals identified as having diagnosed OSA were matched by age, sex, and enrollment date with up to five patients with no OSA diagnosis. The index date was defined as the date of the sleep diagnosis for those exposed, while the index date for the unexposed was the same date as the exposed person to whom they were matched.

Sleep variables

For the primary exposure definition, claims for diagnosed OSA were identified from the inpatient and outpatient databases using the following ICD-9-CM codes: 327.20 (organic sleep apnea, unspecified), 327.23 (obstructive sleep apnea adult pediatric), 327.29 (other organic sleep apnea), 780.51 (insomnia with sleep apnea, unspecified), 780.53 (hypersomnia with sleep apnea), and 780.57 (unspecified sleep apnea). We required that all claims occur after the AF diagnosis. Two sensitivity analyses with different exposures definitions were also performed. One, a more specific definition, required both the above listed ICD-9 codes as well as Current Procedural Terminology (CPT) codes for polysomnography and PAP devices (G8759, G8839, G8846, G8848,

95808, 95810, 95811, G0398, G0399, G0400). The other sensitivity analysis used a broader definition of ICD-9 defined OSA (327.2x and 780.5x) similar to other publications.[313,314] Validation studies comparing ICD-9 codes to polysomnography found codes for polysomnography + PAP device had better performance, with sensitivities ranging from 0.02-0.70 and specificities ranging from 0.36-0.99, depending on definition and data source.[313,314]

Outcome ascertainment

Ischemic stroke was defined using the ICD-9-CM codes 434.xx (occlusion of cerebral arteries) and 436.xx (acute but ill-defined cerebrovascular disease) in the primary position. These algorithms had a positive predictive value of 80% or greater in a systematic review.[315] MI was defined using the ICD-9-CM codes 410.xx in the first or second position. Positive predictive values for this algorithm range from 88-94%.[316,317] Migraines, defined using ICD-9-CM codes 346.xx, were selected as a control outcome, because no association with OSA was expected. Thus, if rates of migraines were different between those with and without diagnosed OSA it would suggest residual confounding.

Covariate ascertainment

Information on pre-determined covariates was identified using claims. In order to have adequate covariate information, a minimum of 90 days of enrollment was required prior to the participant 'index' date. Claims information came from inpatient, outpatient and pharmacy databases, and included information on demographics, comorbidities, and medications. Validated algorithms[318] were used to define pre-specified comorbidities such as depression and alcohol abuse. Prescription medications included hypnotics, anti-

depressants, thyroid medications, smoking cessation medications, and weight loss medications. CHA_2DS_2-VASc score was also calculated.[319]

Analysis

To control for differences between patients with OSA and without OSA and, therefore, reduce confounding, we calculated high-dimensional propensity scores (HDPS) using SAS macros.[320] To assemble these scores, database information was categorized into 5 domains: inpatient diagnostic codes, inpatient procedure codes, outpatient diagnostic codes, outpatient procedure codes, and medications. The algorithm identified the top 200 most prevalent claims from each of the five domains, which resulted in 1,000 covariates. These covariates were ranked based on their potential to control for confounding. In addition to the variables identified by HDPS, we forced the pre-determined covariates described above into HDPS calculation, and ignored potential mediators of the OSA-CVD relationship such as hypertension, heart failure, diabetes, and CHA_2DS_2-VASc. Based on this prioritization, we selected the top 500 variables and included them in a logistic regression model to estimate the probability of OSA exposure. The HDPS was then used to adjust the models as a continuous covariate.

Cox proportional hazards models were used to model time to incident ischemic stroke, MI, and migraine events according to diagnosed OSA status. Person-time was calculated by using the time from the index date until an outcome event, health plan disenrollment, or the end of the follow-up period. For each outcome, models were adjusted for age, sex, pre-specified covariates, and HDPS (continuous). SAS version 9.3 (SAS Institute, Cary, NC) was used to analyze the data.

Exposure misclassification, through the use of ICD code-defined OSA, is unavoidable when using administrative data. We conducted bias analyses[321,322] to estimate rate ratios adjusted for misclassification, using sensitivities and specificities that have been reported in the literature. Because prior literature reported a range of sensitivities and specificities,[313,314] we repeated our bias analysis at sensitivities from 0.02-0.58 and specificities from 0.36-0.99.

Results

The mean age at baseline was 64.8 years and 29.7% of the sample was female. There were 4725 new cases of ischemic stroke and 6500 new cases of MI over an average of 16 months of follow-up. This incidence rate was 6.7 (95% CI 6.5-6.9) stroke cases and 9.3 MI cases (95%CI 9.0-9.5) per 1000 person-years.

Table 5.1 shows characteristics of AF patients by diagnosed OSA status. Due to matching, age and sex were similar in both groups. Compared to those without an OSA diagnosis, a greater proportion of those with an OSA diagnosis had diabetes, heart failure, hypertension, and depression. Additionally, a greater proportion of those with diagnosed OSA had a claim for hypnotics and anti-depressants.

Table 5.2 shows, among AF patients, adjusted hazard ratios and 95% confidence intervals for ischemic stroke, MI and migraines, according to diagnosed OSA status. After adjustment for age, sex, depression, alcohol, medications, and propensity score, an OSA diagnosis was strongly and significantly associated with a reduced hazard of ischemic stroke (HR = 0.59, 95%CI 0.53, 0.66) and MI (HR = 0.49, 95%CI 0.45, 0.54).

Results were similar when OSA was defined by both ICD-9 and CPT codes, as well as when the broad definition of OSA was used.

Table 5.2 also shows adjusted hazard ratios and 95% confidence intervals for migraines, the control outcome by diagnosed OSA status. After adjustment for age, sex, confounders, and propensity score, there was little evidence of an association between OSA diagnosis and migraines (HR= 0.87, 95% CI 0.70, 1.08). Similar results were found with varying definitions of OSA.

Bias analysis was used to evaluate the influence that misclassification of OSA diagnosis based on ICD codes may have had on our results (**Table 5.3)**. Equations[321,322] using estimates of sensitivity and specificity from validation studies[313,314] were used to correct for misclassification, allowing for estimation of expected observed frequencies by exposure (OSA) and outcome (e.g. stroke) category, as well as rate ratios. Application of these equations resulted in some expected observed frequencies having negative values, and therefore errors when attempts were made to calculated relative rates adjusted for misclassification. In exploratory analyses where we randomly selected values from the range of published sensitivities and specificities, without errors, corrected rate ratios ranged from 0.25 to 14.31 (**Table 5.3**).

Discussion

In this analysis of a large administrative database of AF patients, counter to our hypothesis, an OSA diagnosis was associated with a strikingly lower risk of incident stroke and MI. We rigorously attempted to mitigate uncontrolled confounding by using high dimensional propensity scores. Additionally, we incorporated into the analysis a

control outcome, migraines, which showed little evidence of residual confounding. As such, our findings raise questions about whether administrative data can be used to test hypotheses about exposures which are believed to be grossly underdiagnosed, such as OSA.[57] Approximately 85% of individuals who meet the diagnostic criteria for OSA are unaware of their status.[50]

Comparison to prior literature

Previous research exploring the association between OSA and atherosclerotic CVD risk among AF patients are summarized in **Table 5.4**. In one study of 17,000 AF patients, a Taiwanese national health insurance database found no statistically significant association between ICD-9 defined OSA and stroke, though similar to our findings, hazard ratios were in a protective direction (HR~0.80).[311] In a study using the ORBIT-AF registry, OSA defined via clinician diagnosis or history was not associated with a composite cardiovascular outcome, which included cardiovascular death, MI, and stroke/TIA.[310] However, in a small study of patients referred for polysomnography, OSA was strongly associated with first-time stroke among AF patients (OR~3.84).[309] Thus, large studies using administrative or self-reported measures of OSA found protective or no associations, while a study with a small number of cases that used polysomnography found a greatly increased risk of stroke among those with OSA.

Our finding of OSA being associated with decreased atherosclerotic CVD risk is counterintuitive, as pathophysiology suggests that OSA results in the hypoxia, hypercapnia, changes in autonomic nervous system activity, and inflammation, all of which could act in AF patients to increase atherosclerotic CVD risk.[53] Additionally,

epidemiologic studies in 'healthy' population-based samples without AF also suggest that OSA is associated with increased risk of stroke and CHD.[181,308]

Potential influence of measurement error

A plausible explanation for these unexpected results is measurement error in the exposure. The gold standard for measuring OSA is polysomnography; however, this method is too expensive and burdensome to implement in a sample this large. Two papers have examined the validity of administrative data as compared to polysomnography for defining OSA. Applying several different ICD-code definitions of OSA, one sample of Canadian surgical patients found a range of mostly high specificities (e.g. 36-99%) and low sensitivities (e.g. 2-70%) that varied due to the case definition,[313] while a second study of patients referred for sleep studies found that sensitivity decreased and specificity increased when multiple claims were required (e.g. with 1 code the sensitivity = 44-47% and specificity = 39-49%, with multiple codes sensitivities were 12-16% and specificities 82-87%).[314] In a secondary analysis, we tried to increase the specificity of our OSA definition, by requiring both ICD and CPT codes. The low sensitivity of ICD-defined OSA is not surprising given that 85% of individuals who meet the diagnostic criteria for OSA are unaware of their status[50] and approximately two to three times more people experience OSA symptoms than have a diagnosis.[57]

In **Table 5.3**, we attempted to use the published sensitivities and specificities to generate rate ratios adjusted for misclassification, in order to estimate the expected association between OSA and atherosclerotic CVD among AF patients. Unfortunately, applying the published estimates of sensitivity and specificity to the misclassification bias

analysis equations resulted in errors. This incompatibility can occur if the validation data is based on a population with different classification characteristics or there is some form of bias leading to the inconsistency.

On average, non-differential biases results toward the null and correction for nondifferential misclassification results in measures of association further away from the null.[321] In this study, we specified a non-differential misclassification, which would appear unlikely to explain the unusual protective result we found (since the misclassification adjusted result would be even more protective). However, if the sensitivities and specificities add up to less than one, indicating that the classification is worse than random, it is possible for the direction of the association to be reversed, and thus correction for this kind of misclassification could change associations from protective to harmful.[321] Several combinations of sensitivities and specificities from the validation papers add up to less than one, including exposure definitions most similar to the ones used in this study. In addition, our exploratory analysis demonstrates that choosing sensitivities and specificities similar to the published validation figures, that sum to less than one, produce rate ratios suggesting OSA is adversely associated with atherosclerotic CVD among AF patients. As such, it is conceivable that misclassification bias as a result of the low sensitivity and specificity of ICD-defined OSA may have led to our surprising result of OSA being associated with strikingly lower risk of stroke and MI.

The bias analyses we conducted focused on nondifferential misclassification, however, as the validity of defining OSA using ICD codes has not been examined with regard to any outcome, it is possible that measurement error in the OSA exposure is

differential (i.e. different for those with and without CVD in this sample). An example of how differential misclassification could occur is if those who were obese were more likely to be screened for OSA, and also more likely to experience an atherosclerotic CVD event during follow-up. In addition to uncertainty about whether measurement error was differential or non-differential, it is also unclear how the validity of using administrative data to define OSA compares to other measurement methods used in some prior publications in the absence of polysomnography (e.g. self-reported physician's diagnosis of OSA, or snoring as a surrogate).

Potential influence of selection bias

Another possible explanation for our unanticipated results is selection bias. Because participants are older, it is possible that those with OSA had already died of MI or stroke before the beginning of the study. As a result, those with OSA in this study may be healthier and thus less likely to develop atherosclerotic CVD than those in the general population, resulting in the counterintuitive associations. However, in our sample a greater proportion of those with diagnosed OSA compared to those without OSA had diabetes, heart failure, and depression, making this explanation less likely.

Additionally, our unexpected finding that OSA is associated with lower risk of atherosclerotic CVD may be analogous to the established "obesity paradox', where overweight or obese patients are at lower risk for outcomes compared to those who are normal weight. This phenomenon has been has been documented for some CVD events in AF patients.[323] Selection bias is one plausible explanation for this sort of occurrence, due to conditioning on a collider.[324]

Strengths and additional limitations

Other limitations of this study include the possibility that those diagnosed with OSA may also have received treatment over the follow-up period, which may have reduced the incidence of stroke or MI. However, though OSA treatment such as CPAP improves OSA and daytime sleepiness,[325,326] adherence is low as patients do not always find the treatment acceptable.[117,120] Thus, those prescribed treatment may not be at reduced risk. In the MarketScan dataset information on some potential confounders (e.g. BMI) was not present, however high-dimensional propensity score methodology helped to control for residual confounding.[320] Besides the use of propensity scores, other strengths of this study include a large real world sample with extensive information on medications and comorbidities.

Conclusions

In this study, diagnosed OSA was strongly associated with reduced risk of incident atherosclerotic CVD, a counterintuitive finding possibly attributable to error in the measurement of OSA. More longitudinal studies or trials with valid and reliable measurements of sleep apnea are thus needed to provide more definitive evidence on this association. The present findings also raise questions about the validity of research using administrative data to define OSA, and possibly other exposures that are known to be highly underdiagnosed.

Table 5.1: Characteristics of atrial fibrillation patients by sleep apnea status, MarketScan 2007-2014

	Sleep apnea (ICD)*	No Sleep apnea
N	90,274	446,903
Age	64.6 ± 11.9	64.8 ± 12.0
>65	21,130 (23.4)	107,319 (24.0)
>75	20,295 (22.5)	102,186 (22.9)
% Female	26,407 (29.3)	133,317 (29.8)
CHA_2DS_2-VASc score	2.4 ± 1.9	2.3 ± 1.9
Diabetes	23,367 (26.2)	92,052 (20.6)
Heart Failure	21,670 (24.0)	80,275 (17.8)
Ischemic Stroke	10,451 (11.6)	52,924 (11.8)
Hypertension	50,743 (56.2)	232,110 (51.9)
Vascular Disease	13,392 (14.8)	65,938 (14.8)
History		
Comorbidities		
Depression	7,528 (8.3)	31,216 (7.0)
Alcohol abuse	339 (0.4)	2,663 (0.6)
Medications		
Hypnotics	8.337 (9.2)	33,742 (7.6)
Anti-depressants	17,621 (19.5)	69,670 (15.6)
Varenicline	468 (0.5)	2,318 (0.5)
Weight loss medication	773 (0.9)	1,963 (0.4)
Thyroid medication	10,284 (11.4)	46,645 (10.4)

*Primary exposure definition

Table 5.2: Adjusted hazard ratios (95% confidence intervals) for atherosclerotic cardiovascular disease by sleep apnea among patients with atrial fibrillation: MarketScan 2007-2014

	OSA ICD Only (Primary definition)		OSA ICD + CPT (More specific definition)		OSA Broad ICD (Less specific definition)	
	No OSA	OSA	No OSA	OSA	No OSA	OSA
Ischemic Stroke						
N Events	4,023	702	1,192	203	5,376	1,159
N Total	446,903	90,274	130,826	25,942	575,347	124,287
Model 1	Ref.	0.58 (0.53, 0.63)	Ref.	0.59 (0.51, 0.68)	Ref.	0.60 (0.56, 0.64)
Model 2	Ref.	0.57 (0.53, 0.62)	Ref.	0.57 (0.49, 0.67)	Ref.	0.60 (0.56, 0.64)
Model 3	Ref.	0.59 (0.53, 0.66)	Ref.	0.56 (0.45, 0.68)	Ref.	0.71 (0.66, 0.76)
Myocardial Infarction						
N Events	5,619	881	1,656	273	6,903	1,250
N Total	446,903	90,274	130,826	25,942	575,347	124,287
Model 1	Ref.	0.53 (0.49, 0.57)	Ref.	0.58 (0.51, 0.66)	Ref.	0.51 (0.48, 0.55)
Model 2	Ref.	0.53 (0.49, 0.56)	Ref.	0.57 (0.50, 0.65)	Ref.	0.52 (0.49, 0.55)
Model 3	Ref.	0.49 (0.45, 0.54)	Ref.	0.47 (0.40, 0.55)	Ref.	0.48 (0.45, 0.51)
Migraine						
N Events	859	216	266	75	869	310

N Total	446,903	90,274	130,826	25,942	575,347	124,287
Model 1	Ref.	0.86 (0.74, 1.00)	Ref.	1.06 (0.82, 1.37)	Ref.	0.99 (0.87, 1.13)
Model 2	Ref.	0.81 (0.69, 0.94)	Ref.	1.01 (0.78, 1.31)	Ref.	0.89 (0.78, 1.02)
Model 3	Ref.	0.87 (0.70, 1.08)	Ref.	0.88 (0.60, 1.30)	Ref.	1.00 (0.87, 1.15)

Abbreviations – OSA: obstructive sleep apnea, ICD: International Classification of Diseases, CPT: Current Procedural Terminology
Model 1 adjusted for age and sex
Model 2 added depression, alcoholism, sleep medications, anti-depressants, thyroid medication, weight-loss medication, and anti-smoking medication
Model 3 added continuous high dimensional propensity score

Table 5.3: Bias analysis for the association between OSA and risk of ischemic stroke using sensitivities and specificities for OSA defined by ICD codes versus gold-standard polysomnography*

		Sensitivity	Specificity	Corrected Rate Ratio
Current data	Primary OSA definition: ICD-9-CM codes 327.20, 327.23, 327.29, 780.51, 780.53, 780.57	Observed	Observed	0.58
Sensitivities and specificities from McIsaac, et al[313]	Polysomnography + prescription for CPAP	0.19	0.98	Error: negative cell*** (-0.60)
	ICD-10: 4730 (hospital discharges)	0.07	0.99	Error: negative cell (1.28)
	ICD-10: G4738 (hospital discharges)	0.02	0.99	Error: negative cell (1.03)
	Any ICD-10 code (hospital discharges)	0.09	0.98	Error: negative cell (1.46)
	ICD-9 780.5 (hospital discharges)	0.03	0.98	Error: negative cell (1.03)
	ICD-9 780.5	0.58	0.38	Error: negative cell (0.98)
	Polysomnography + PAP or any ICD code	0.70	0.36	Error: negative cell (1.02)
Sensitivities and specificities from Laratta, et al[314]	RDI $\geq 5\ h^{-1}$ 1 claim or discharge code (780.5)	0.465	0.394	Error: negative cell (0.90)
	RDI $\geq 5\ h^{-1}$ 2 claims or discharge codes (780.5)	0.241	0.678	Error: negative cell (0.22)

	RDI ≥ 5 h^{-1} 3 claims or discharge codes (780.5)	0.124	0.817	Error: negative cell (-3.14)
	RDI ≥ 15 h^{-1} 1 claim or discharge code (780.5)	0.442	0.464	Error: negative cell (0.91)
	RDI ≥ 15 h^{-1} 2 claims or discharge codes (780.5)	0.260	0.746	Error: negative cell (1.19)
	RDI ≥ 15 h^{-1} 3 claims or discharge codes (780.5)	0.138	0.866	Error: negative cell (1.32)
	RDI ≥ 30 h^{-1} 1 claim or discharge code (780.5)	0.442	0.490	Error: negative cell (0.93)
	RDI ≥ 30 h^{-1} 2 claims or discharge codes (780.5)	0.285	0.753	Error: negative cell (2.38)
	RDI ≥ 30 h^{-1} 3 claims or discharge codes (780.5)	0.164	0.874	Error: negative cell (-0.93)
Exploratory sensitivities and specificities				
		0.57	0.89	0.26
		0.11	0.59	4.55
		0.14	0.54	14.31
		0.05	0.38	2.22
		0.52	0.89	0.25
		0.03	0.69	3.43

		0.07	0.69	4.14
		0.50	0.92	0.35
		0.07	0.71	4.85
		0.04	0.42	2.16
	Excel tables used for calculations obtained from https://sites.google.com/site/biasanalysis/ RDI – respiratory disturbance index, OSA – obstructive sleep apnea, CPAP – continuous positive airway pressure *Estimates from published validation studies **Primary exposure definition *** Negative cells indicate false positive proportion is higher than the prevalence of OSA among those with cardiovascular disease			

Table 5.4: Summary of previous studies on OSA and atherosclerotic cardiovascular disease among atrial fibrillation patients

Authors	Sample Size	AF Population	Measurement of OSA	Outcome	Length of follow-up	Results
Current study	100,000 +	U.S. Administrative Claims data	ICD-9	Stroke and myocardial infarction via ICD-9	~ 500 days	HR~0.60
Chang et al.[311]	17,375	Taiwan health insurance claims	ICD-9	Stroke via ICD-9	2.5 years	HR~0.80
Holmqvist et al.[310]	10,132	ORBIT-AF registry	Physician report and medical records	Composite of cardiovascular death, coronary heart disease, stroke/TIA	2 years	HR~1.10
Yaranov et al.[309]	332	Patients referred for sleep study	Polysomnography	Stroke via electronic medical records	4.4 years	OR~3.84

Conclusions

Sleep problems, including short sleep duration and OSA, are prevalent and associated with a variety of adverse health outcomes. The objective of this dissertation was to explore the relationship between these sleep disturbances and cardiometabolic risk factors and outcomes. Manuscripts 1 and 2 examined the relationship between sleep duration related indices and eating and obesity, while manuscripts 3 and 4 focused on OSA and risk of atherosclerotic cardiovascular events.

Manuscript 1

Although young adults are particularly likely to fail to meet published sleep duration recommendations,[8] few studies have evaluated the influence of sleep on health in this age group. In manuscript 1, we examined the cross-sectional association between several sleep indices and risky eating behaviors in young adults. Late sleep timing was most consistently associated with poor eating behaviors, including consumption of energy drinks, sugar-sweetened beverages, fast food and breakfast skipping, while fewer associations were found for the other sleep indices (i.e. time in bed, sleep quality, and sleep variability). The inconsistencies across indices may indicate measurement error or may represent unique independent dimensions of sleep. However, these findings must be interpreted cautiously, as the study was cross-sectional and the causal pathway may be bidirectional.

Manuscript 2

Among older adults, prior research on sleep and obesity has been limited by self-reported measures of a single sleep index and racially and ethnically homogenous populations. In manuscript 2, we examined the cross-sectional association between objectively measured sleep indices and adiposity among older adults in MESA. Those sleeping less than 5 hours per night had higher BMIs, larger waist circumferences, and more kilograms of body fat than those who slept 7-8 hours a night. Those with low sleep efficiency and high sleep variability also had higher BMIs, larger waist circumferences, and more body fat, though associations were smaller after adjustment for sleep duration. Combined, both manuscripts 1 and 2 demonstrate the importance of examining sleep indices beyond just sleep duration or time in bed, though both analyses were cross-sectional, thus the temporal nature of the relationship is unclear.

Manuscript 3

Although daytime sleepiness is the most common symptom of OSA,[275] neither the relationship between OSA and daytime sleepiness, nor the impact of presenting with both OSA and daytime sleepiness, is well understood. The aim of manuscript 3 was to determine if there was a joint effect and/or a statistical interaction between daytime sleepiness and OSA in relation to incident CVD, including CHD and stroke, in the prospective SHHS. Although there were small associations for OSA and daytime sleepiness that did not always reach statistical significance, we found no evidence of a statistically significant interaction between daytime sleepiness and OSA on either the

additive or multiplicative scales, and no meaningful joint associations, indicating that measuring both sleep characteristics provides little additional information about CVD incidence.

Manuscript 4

Although OSA has been associated with AF,[179,303,304] and stroke and MI are common outcomes among AF patients,[300-302] the few studies examining the relationship between OSA and atherosclerotic CVD in AF patients have reported mixed results. In manuscript 4, we examined the association of OSA and atherosclerotic CVD among patients with AF in a large administrative claims database. Contrary to our hypothesis, we found that an OSA diagnosis was associated with a lower risk of incident stroke and MI, even after using high dimensional propensity scores to control for residual confounding. It is possible that these findings are attributable to either measurement error or selection bias.

Overall conclusions

Overall, this dissertation provides cross-sectional and longitudinal information about the associations between sleep characteristics and cardiometabolic disease in both younger and older adults, using a variety of measurements to assess sleep. The findings in these manuscripts have enhanced the understanding of these sleep quality, sleep quantity, and CVD risk factors and outcomes.

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