Chronic Sleep Disturbances, Type II Diabetes and Dietary Intake; an Assessment of Gender-Based Differences.

by

Heidi M. Guyer

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2018

Doctoral Committee:

Associate Professor Ana Baylin, Chair
Research Professor Philippa Clarke
Professor Siobán Harlow
Research Scientist Steven Heeringa
Research Professor Kenneth Langa

Heidi M. Guyer

hguyer@umich.edu

ORCID iD: 0000-0001-7621-2972

Dedication

I dedicate this dissertation to my family, friends and colleagues who have provided much needed support in this journey. Especially in mind are those of you who suffer from poor quality sleep and other chronic health conditions, such as diabetes. Despite the ever-changing and evolving world we live in, it's important to pay on-going attention to our most basic biological needs- quality sleep, a healthy diet and physical activity- as well as our emotional and mental needs through a supportive network of family and friends, healthy relationships, open communication and keeping the peace throughout it all. May this endeavor provide inspiration to my children, my nieces and nephew, and other family members.

Acknowledgements

First and foremost, I must acknowledge the support, guidance, knowledge and patience of my mentor and committee Chair, Dr. Ana Baylin. Her continued encouragement over these past few years was exactly what I needed in order to accomplish this incredible achievement. I would also like to acknowledge my committee members Dr. Philippa Clarke, Dr. Siobán Harlow, Dr. Steve Heeringa and Dr. Ken Langa, each whom have shared their knowledge and offered honest feedback along the way. My colleagues and friends at the University of Michigan's Survey Research Operations (SRO) unit of the Survey Research Center have also provided much needed encouragement and motivation along the way. Specifically, Dr. Kirsten Alcser's on-going interest in my research and support of my goals has been greatly appreciated. My cohort of epidemiology PhD students have also been a source of support over the past five years and I truly look forward to our continued collaborations in the years ahead.

Table of Contents

Lists of Tables

Lists of Figures

Abstract

Chronic sleep disturbances are associated with the development and progression of chronic conditions such as cardiovascular disease, hypertension, obesity and cancer. Sleep disturbances are categorized as exceptionally short or long sleep duration as well as difficulty falling asleep or difficulty maintaining sleep. The prevalence and incidence of type II diabetes increased three-fold among adults in the United States between 1980 and 2012. The goals of this research are to assess the bidirectional association between chronic sleep disturbances and diabetes among older adults, by gender, as well as the joint effects of diabetes and chronic sleep disturbances on healthy dietary consumption.

Participants were selected from the Health and Retirement Study, a longitudinal, nationally representative sample of individuals over the age of 50 in the United States. Multivariate Cox-proportional hazard models were used to assess the association between chronic sleep disturbances and development of diabetes within eight years of follow up.

Women who reported chronic sleep disturbances at baseline (2006) had a 27% greater hazard of developing diabetes within eight years than those without chronic sleep disturbances (OR 1.37; 95% CI 1.17-1.60). The association was attenuated after multivariable adjustment for time-varying covariates yet was still significant (OR 1.27; 95% CI 1.08-1.50). While the association was in the same direction in men, it was not statistically significant (adjusted for time-varying covariates OR 1.14; 95%CI 0.88-1.48). In assessing the relationship between newly

identified cases of diabetes and the development of sleep disturbances, women with newly reported diabetes were 80% more likely to develop a chronic sleep disturbances after four years than those without diabetes (OR 1.80, 95% CI 1.01-3.20). However, the association was attenuated and no longer significant after multivariable adjustment (OR 1.63; 95% CI 0.86-3.12). While it does appear that men with newly reported diabetes have a slightly higher odds of developing chronic sleep disturbances, the results do not reach statistical significance (multivariable adjusted OR 1.14; 95%CI 0.69-1.90).

In assessing the associations between the comorbidity of chronic sleep disturbances and diabetes on consumption of a healthy diet, defined as a Mediterranean diet, men with diabetes appear to consume a healthier diet unless they have a chronic sleep disturbance. Women with diabetes do not appear to consume a healthier diet and those with diabetes and chronic sleep disturbances are 20% less likely to consume a healthy diet than those without diabetes or chronic sleep disturbances. Sleep disturbances appear to have an antagonistic association with diabetes and adherence to a healthy diet in both women and men.

In conclusion, our research shows that chronic sleep disturbances, specifically trouble falling asleep or staying asleep, are associated with the onset of diabetes in women, women with diabetes are somewhat more likely to develop chronic sleep disturbances within four years of receiving a diagnosis of diabetes, and that chronic sleep disturbances have a negative association with healthy dietary intake among those with diabetes. Additionally, our research shows that women report greater rates of sleep disturbances and the relationship between sleep disturbances and diabetes varies by gender as well as by race and ethnicity. Novel aspects of this research include the findings related to self-reported sleep quality, rather than sleep duration, as well as the quantification of differences by gender and race/ethnicity. In an increasingly aging, diverse

population, understanding the impact of sleep disturbances in the onset and progression of diabetes elucidates an important area for prevention as well as detection and treatment at the individual level as well as the population-level.

Chapter 1 Introduction

Background

Diabetes mellitus is a chronic condition that takes a considerable toll at the individual and societal level. Diabetes is the most frequently diagnosed chronic condition and the chronic disease that is increasing at the most rapid rate in the world (1). Between 1980 and 2008, the U.S. population age 65 and older experienced the greatest increase in the prevalence of diabetes with an increase from 8% to nearly 20%, indicative of the global pandemic of diabetes (2). Between 2008 and 2012, the prevalence of diabetes plateaued in the U.S. with the exception of specific subgroups of the population that continued to experience an increase in incidence and prevalence. This included younger adults, those with a high school education or less, and Hispanic as well as non-Hispanic black adults (3-5). Differences in the prevalence of diabetes due to age and gender have been reported as well. In the United States, the prevalence of diabetes increases through age 74, with the greatest increases during older adulthood (ages 45-74) after which the prevalence remains relatively stable (2). Diabetes is more prevalent in men than women, with the exception of women age 80 and over in which diabetes is slightly higher in women (1%), likely due to increased longevity in women and increased diabetes in this older age group. While age and gender are non-modifiable risk factors for the development of type II diabetes, modifiable lifestyle factors are largely responsible for the increase in type II diabetes (2). These lifestyle factors are primarily due to increased caloric consumption, characterized by simple carbohydrates and high sugar content, and decreased physical activity- an energy

imbalance- leading to obesity. However, these traditional lifestyle behaviors do not fully explain the increased incidence of type II diabetes, nor does family history or, genetics.

Individuals with diabetes are likely to have multiple chronic conditions. Comorbidity with hypercholesteremia, hypertension, obesity, heart disease and stroke is not uncommon among those with diabetes. Chronic conditions can also be the result of diabetes including conditions such as kidney disease, blindness and neuropathy. Additionally, individuals with diabetes are more likely to develop physical and cognitive disabilities such as dementia (2). Thus, not only is diabetes itself a concern, but the high rate of associated comorbid conditions leads to greater concern, and greater cost.

The costs associated with diagnosed diabetes are staggering. In 2008, it was estimated that one out of every five dollars spent on health care in the United States was spent on diabetic patients (6). The total estimated cost of diagnosed diabetes was $174 billion in 2007. In 2012, it was estimated that the total annual cost of diagnosed diabetes had increased to $245 billion, a 41% increase in five years. Seventy-two percent (72%) of the $245 billion was attributable to direct medical costs and the remainder due to lost productivity. At the individual level, the total annual health care costs of those with diagnosed diabetes are close to $14,000, likely due to the increased risk of comorbid conditions in this population. Close to $8,000, or 58% of the annual medical costs incurred were attributable to the diagnosed diabetes, including doctor's visits, medical tests and medication. These increased health care costs are likely to come at a time in life in which health care coverage is extremely expensive and prescription coverage is limited for a large portion of the affected population. Two-thirds of these costs are covered by the government (Medicare, Medicaid, the military) and by uninsured individuals (3.2%). With the

cost of insulin increasing three-fold in the last ten years, the undue burden on our aging population must be addressed (7).

The daily goal of those with diabetes is to maintain glycemic levels within a healthy range in order to reduce the deleterious potential effects of this treatable, but incurable, chronic disease. Dietary intake, physical activity, obesity and medication all affect glycemic levels. As the population-based prevalence of diabetes and obesity have increased over the past thirty years, chronic sleep disturbances have increased as well (8). Sleep disturbances can lead to metabolic dysfunction/deregulation, poor glycemic control and reduced insulin sensitivity. Sufficient sleep quantity as well as sleep quality helps to achieve and maintain healthy glucose levels as well as decrease insulin resistance.

Numerous cross-sectional studies have reported increased rates of sleep disruptions, including short sleep duration, among adults with diabetes compared to those without diabetes (9-17). Women tend to report greater levels of comorbidity of diabetes and chronic sleep disturbances than men. Several longitudinal studies have provided evidence that inadequate sleep duration or sleep disturbances are associated with the development of diabetes (18-20). Most of these studies have been conducted outsides of the U.S. and gender-based differences have not been reported.

Little is known about the degree to which those who previously did not have sleep disturbances are likely to develop a chronic sleep disturbance after a recent diagnosis of diabetes. This is an important question to address as chronic sleep disturbances appear to increase the risk of poor glycemic control and insulin sensitivity (21). While it is plausible that there is an initial period of increased sleep disturbances related to the anxiety of a new diagnosis, and incorporating new behaviors and medications into one’s lifestyle, it is not known whether new

sleep disturbances continue well past the initial diagnostic and medication regulation phase. Sleep disturbances can lead to metabolic deregulation and decrease one's likelihood to adhere to dietary restrictions (21). This dissertation will provide new information on whether chronic sleep disturbances modify the association between diabetes and dietary intake and lead to lower adherence to a healthy diet, assessed using a Mediterranean-style diet score.

Sleep architecture

Humans have a basic biologic need for sleep. Sleep is necessary for the maintenance of our physical and cognitive health (22). An increasing emphasis has been placed on the epidemiology of sleep in recent years to better understand the associations between sleep quality and duration and health (23-25). With sleep disturbances on the rise, and societal changes that seem to promote decreased sleep, knowledge of the associated risks is becoming increasingly important.

Sleep architecture refers to the stages of sleep and the cycles that occur throughout the night. While the focus of this dissertation is on overall self-reported sleep quality, rather than disruptions in sleep stages, it is important to understand sleep architecture as it relates to the development of chronic conditions. Briefly, there are 4 stages of sleep that comprise a cycle and each cycle is approximately ninety (90) minutes in duration. The stages are:

Light sleep - stages 1 and 2. Stage 1 is marked by drowsiness while still being conscious whereas in stage 2, you are just beginning to slip into sleep. During light sleep, you are easily awoken and will remember being awoken. Adults typically spend 40-60% of total sleep time in this stage.

Deep sleep - stages 3 & 4. Stage 3 is marked by slowed breathing, slowed heart rate and lower body temperature. Stage 4 is considered deep sleep, or slow wave sleep (SWS). During

this stage, it is very difficult, if not impossible, to wake someone up. If awoken, the individual may not remember the awake episode the next day. Deep sleep is considered restorative and important for our health. Adults typically spend 12-18% of their time sleeping in this stage.

Rapid Eye Movement (REM)-stage 5. Stage 5 is the dream stage as this is when dreams occur. During this stage, brain activity increases, heart rate increases and limbs are paralyzed. It is difficult, but not impossible, to be awoken during this stage. REM occurs later at night and is associated with mood and memory. Adults typically spend 15-25% of their sleeping time in this stage.

Awake. While this is not a stage of sleep, it is not uncommon to experience several episodes of brief periods of awakening throughout the night. Many of these episodes are not recollected the following day as they are so brief. Frequent wakening throughout the night is a primary symptom of sleep apnea. Poor sleep quality is marked by waking up after falling asleep and not being able to fall back asleep.

Over the course of the night we typically cycle from light sleep to deep sleep, back to light sleep, and then to stage 5, REM. These cycles occur approximately 5-6 times per night with the duration of deep sleep typically increasing with each cycle. While it is important to cycle through each of the stages in the course of a night's sleep, the amount of time spent in each stage varies and changes over time. As individuals age, less time in deep sleep is required and more time spent in light sleep or episodes of being awake occur. In general, we spend approximately one-third of our lives sleeping, although the required duration of sleep varies from one person to the next. Additionally, the amount of sleep required on a daily basis varies by individual and decreases with age (22, 26).

Sleep and metabolism

Glucose regulation is affected by the sleep-wake cycle with increases in glucose levels found to occur during stages 2-4, or non-REM sleep, and declines in blood glucose levels during periods of being awake (21). During REM sleep, glucose levels remain stable. Thus, natural variation in glucose levels are observed over the course of a sleep cycle. Insulin levels follow a similar pattern to glucose levels. Studies of sleep disruption have found disturbances in glucose levels and insulin regulation to occur after sleep disruptions of just a few nights. Disruption to sleep cycles, specifically reductions in short wave sleep, can lead to disruptions in glucose levels thus potentially increasing the risk of glucose intolerance and incident diabetes over prolonged periods of disruption (27-29).

Sleep disturbances have also been shown to impact the hormones that regulate appetite, such as leptin and gherlin, as well as stimulate an increased appetite for high carbohydrate foods. Several studies have shown disruptions in leptin and gherlin, two hormones that influence appetite, after sleep deprivation and sleep disturbances were controlled in experimental settings (30-33). Additionally, food cravings for high carbohydrate foods, such as sweet or salty snack foods and starchy foods, were increased after sleep deprivation. (34, 35). After these experimental conditions, caloric intake from regular meals stayed the same as during usual, uninterrupted sleep duration, but caloric intake from snacks increased by close to 500 kcal. If chronic sleep disturbances lead to chronic over-consumption of unhealthy foods, an increased risk of obesity will ensue. Additionally, Vgontzas et al found that reduced sleep over the course of one week resulted in increased inflammation, also risk factors for insulin resistance and diabetes (36).

Sleep and diabetes

Recent studies have examined the association between chronic sleep disturbances and the development of type II diabetes. A systematic review by Cappuccio and colleagues (18) found that both sleep duration and sleep quality predict the risk of developing type II diabetes. The review included ten studies and found the greatest risk among those who reported difficulty initiating sleep (RR 1.57; 95% CI 1.25-1.97) and difficulty maintaining sleep (RR 1.84; 95% CI 1.39-2.43). However, the review was unable to report differences in risk by gender or by race/ethnicity and sleep quality in women was only assessed in studies conducted outside of the U.S.. Meisinger and colleagues (10) found that difficulty maintaining sleep was associated with a higher risk of developing type II diabetes among adults age 25-74 with an average follow-up of 7.5 years. The hazard ratio was greater in women than men (women HR 1.98; 95% CI 1.20-3.29; men HR 1.60; 95% CI 1.05-2.45). However, difficulty initiating sleep was not significantly associated with developing diabetes in men or women. The study population included participants from the MONICA study conducted in Germany, a racially and ethnically homogenous population. Hoevenaar-Blom and colleagues (37) found that short sleep duration accompanied by sleep disturbances increased the risk of incident cardiovascular disease after 10-15 years of follow up. However, this study was a population-based study in the Netherlands and was unable to detect or report differences by gender or race/ethnicity.

Disparities in sleep duration and sleep quality have been identified for women, compared to men, and among Black adults compared to white and Hispanic adults (12, 14, 38-46). Numerous studies, primarily cross-sectional, have examined the association between sleep duration, and to a lesser degree sleep quality, and incident diabetes in adult populations (9-20, 47, 48). Yet, a gap exists in the current literature in the role of poor sleep quality and diabetes

among a nationally representative, longitudinal, sample of multi-ethnic older women and men. Most studies to date are of populations of European or Asian descent and few have sufficient sample sizes of Black or Hispanic populations to report associations among these subgroups. Given the higher rates of sleep disturbances reported by Black adults and the higher rates of obesity, hypertension and type II diabetes among Black and Hispanic adults, understanding the role of sleep disturbances in the development of diabetes could provide information that has both clinical relevance as well as important public health implications. Given the aging population, shifting demographics and the increase in type II diabetes in the United States, there is a need to examine these associations differentially by gender as well as by race/ethnicity within gender. Numerous studies have reported increased rates of sleep disturbances among Black and Hispanic adults in the U.S. population. Many of these focus on psychosocial stressors and socio-economic conditions associated with sleep disturbances. The Multi-Ethnic Study of Atherosclerosis (MESA) included 2230 participants with an average age of 68.8 years (39). Multiple measures of sleep quality were used including polysomnography, actigraphy and a self-reported questionnaire. Chen and colleagues found that Black participants had higher rates of sleep apnea, short sleep, poor sleep quality and daytime sleepiness than whites. Hispanic participants had higher odds of sleep apnea and short sleep. Black men and Hispanic women were more likely to report poor sleep quality. The odds of poor sleep quality decreased with age in Blacks but increased among Hispanics. While this study concludes that Blacks and Hispanics may be at an increased risk for the development of chronic conditions related to poor sleep, the association between chronic conditions and sleep disturbances was not assessed in this cross-sectional study.

To our knowledge, no studies have assessed the development of chronic sleep disturbances after the diagnosis of type II diabetes using longitudinal data. The development of

new sleep disturbances is important to assess as poor quality sleep could lead to higher glycemic levels. Several cross-sectional observational studies have found higher hemoglobin A1C (HbA1c) levels, a measure of glycemic control, among those with diabetes who also report short sleep or sleep disturbances (11, 45, 47).

Sleep and dietary intake; Mediterranean diet

The Mediterranean diet has been identified as a plant-based dietary pattern that is associated with healthy aging, improved glycemic control and reduced insulin resistance in healthy populations, as well as in those with cardiovascular disease including hypertension and diabetes (49,50). Plant-based diets that are naturally high in polyphenols and low in saturated fats are also associated with decreased inflammation (51-54). Recent evidence also supports the role of the Mediterranean Diet in improving the gut microbiome thereby reducing inflammation and potentially improving glycemic control as well (55,56). The Mediterranean diet is considered a healthy diet for those with diabetes and meets the key dietary criteria outlined by the American Diabetes Association as it is naturally low in saturated fats, highly processed foods and refined carbohydrates.

In 2003, Trichopoulou and colleagues developed a score based on previous studies of the qualities and benefits of a Mediterranean diet (57-60). During this time, Willett and colleagues described a new food pyramid based on the Mediterranean diet (59). The development of food scores allowed for the focus on intake of individual food items, such as olive oil or fish, as well as an overall healthy dietary pattern. Dietary patterns of multiple food components may provide more information regarding the antagonistic and synergistic effects of consuming a variety of foods. The score developed by Trichopoulou and colleagues is useful in assessing the degree of consumption of Mediterranean diet. Ten components of the diet were identified: cereals,

potatoes, fruits and nuts, vegetables, legumes, fish, meat, dairy products, olive oil, potatoes and eggs. Each of the ten components were assigned a score ranging from 0 to 1 based on gender-specific median values. A score could then be calculated for individuals ranging from 0 to 9 with 0 representing no consumption of a Mediterranean diet and 9 representing the highest level of consumption across all eleven categories of the Mediterranean diet. The score was later revised to include nine components. Potatoes, poultry and dairy products were removed from the score, nuts were added as a separate component, and olive oil was replaced by a ratio of monounsaturated to saturated fats. The replacement of olive oil consumption with a ratio of monounsaturated fats to saturated fats score facilitates the translation of this component to non-Mediterranean populations given the lower intake of olive oil. Additionally, moderate consumption of alcohol was added as a beneficial component. This score is referred to as the alternate Mediterranean diet (aMedDiet) and ranges from 0 to 9, with 9 being indicative of greater adherence to a Mediterranean-style diet. A score of one is given on any component for consumption above the median intake, with the exception of alcohol consumption and red/processed meat consumption. The indices are created separately for men and women given the variation in dietary intake and caloric intake by gender. Thus, median values are calculated separately for men and women and the score is calculated by gender. Samieri and colleagues assessed the relationship between the aMedDiet and healthy aging among participants of the Nurses' Health Study (NHS) who were free of chronic conditions at baseline (61). They found that healthy agers, those who remained free of chronic conditions, were more likely to consume an aMedDiet in the highest quintile of consumption compared to usual agers. DeKoning and colleagues assessed the risk of developing diabetes among participants in the Health Professionals Follow Up Survey (HPFS) who consumed an aMedDiet in the highest quartile

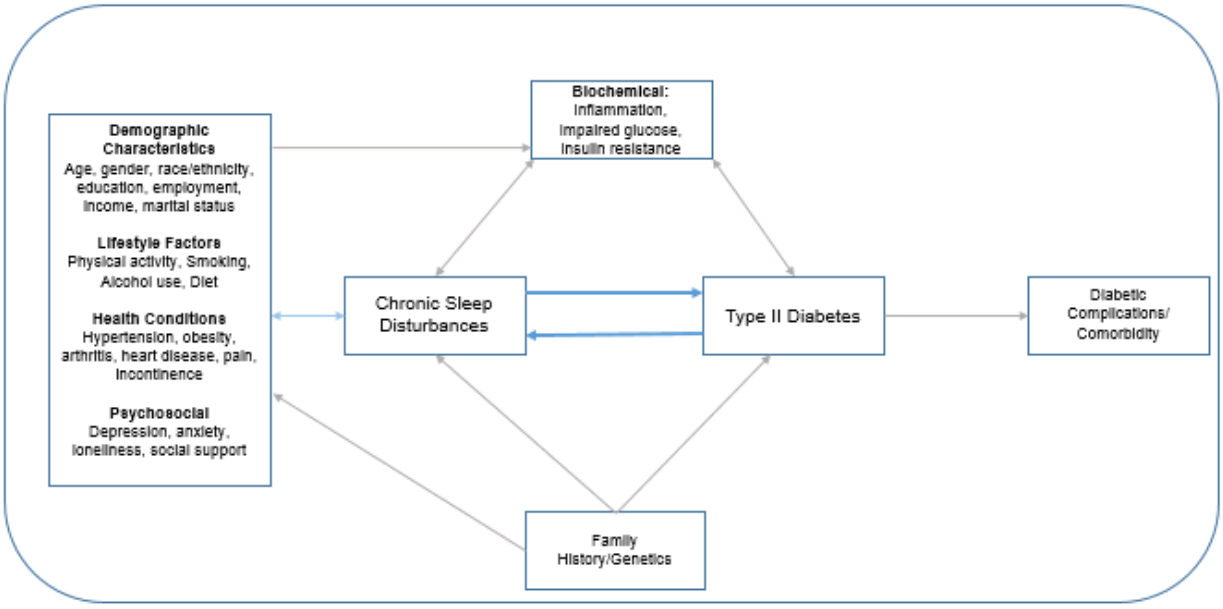
compared to those in the lowest quartile (62). A lower risk of developing type 2 diabetes was found among those who consumed a healthier diet, such as the aMedDiet, than those who did not. While the aMedDiet has been studied among populations at risk of developing or those already diagnosed with a chronic condition, to our knowledge, the effect of comorbidity of chronic sleep disturbances and diabetes on consumption of a Mediterranean-style diet has not been assessed (63-66).

Conceptual Framework and Specific Aims

Conceptual framework

The following diagram depicts the conceptual framework of the association between sleep disturbances and diabetes. Obesity is a primary confounder as it is associated with both the development of sleep disturbances as well as the development of diabetes. Obesity will be included as a confounder in each of the three aims. Unregulated glucose levels, reduced insulin sensitivity and increased inflammation are intermediate variables on the causal pathway in the development of diabetes. These variables were not assessed in the current study. Other demographic, socio-economic, health and psychosocial factors will be included as covariates in assessing the bi-directional relationships between chronic sleep disturbances and incident diabetes. Family history of diabetes is currently an unmeasured confounder in our studies. Future studies could include genetic information related to the increased risk of developing diabetes.

Figure 1.1 Conceptual framework of the bidirectional association of chronic sleep disturbances and type II diabetes.



Single-headed arrows represent an association in one direction. Double-headed arrows represent an association in both directions. Gray arrows indicate unmeasured confounders, intermediate variables or outcomes that are not included in our statistical models (biochemical, diabetic complications/comorbidity and family history/genetics). Heavier blue arrows indicate the primary relationship of interest: the bidirectional association between chronic sleep disturbances and type II diabetes. Lighter blue arrows indicate relationships between covariates.

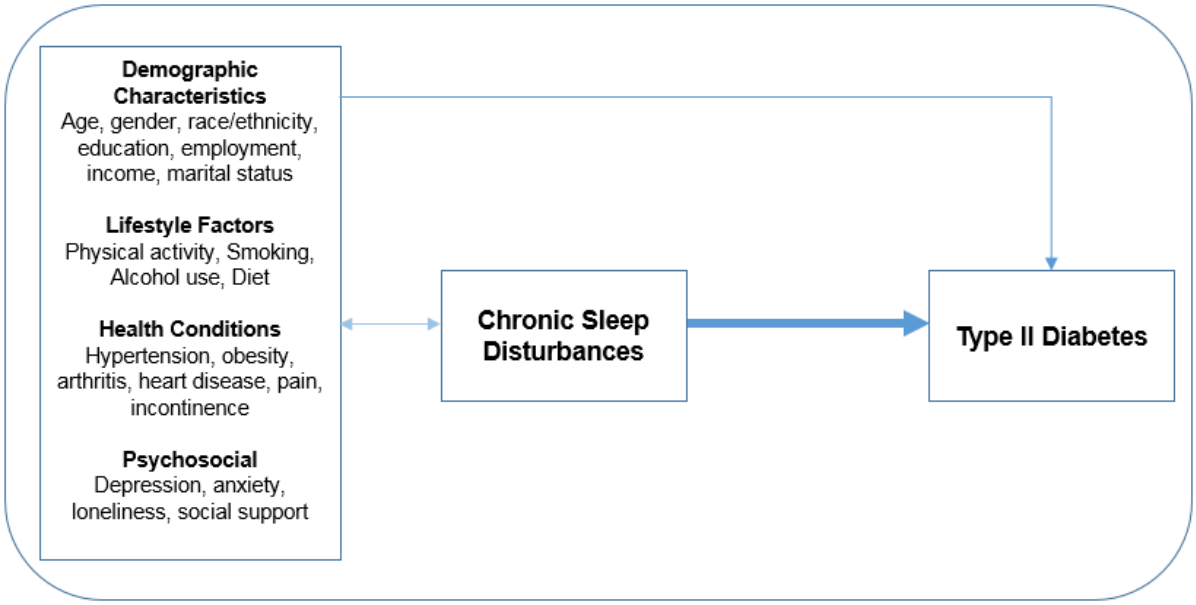
Specific Aims

This dissertation will characterize the bi-directional association of chronic sleep disturbances and newly reported type II diabetes among a national, multi-ethnic sample representative of adults aged 50 and older residing in the United States. First, this study will utilize longitudinal data from the Health and Retirement Study (HRS) to examine the relationship between poor sleep quality and incident diabetes over an eight-year period from 2006 to 2014 (67-70). Next, the association between newly reported type II diabetes and the development of chronic sleep disturbances over a four-year period will be assessed. Finally, this study will assess the association of poor sleep quality with dietary intake among adults with, and without, diabetes based on self-reported consumption of a Mediterranean-style diet (71-72). Differences by gender will be assessed for each of the three aims.

Aim 1. Determine the association between chronic sleep disturbances and incident type II diabetes.

a) Are baseline sleep problems associated with incident type II diabetes over the coming eight years?

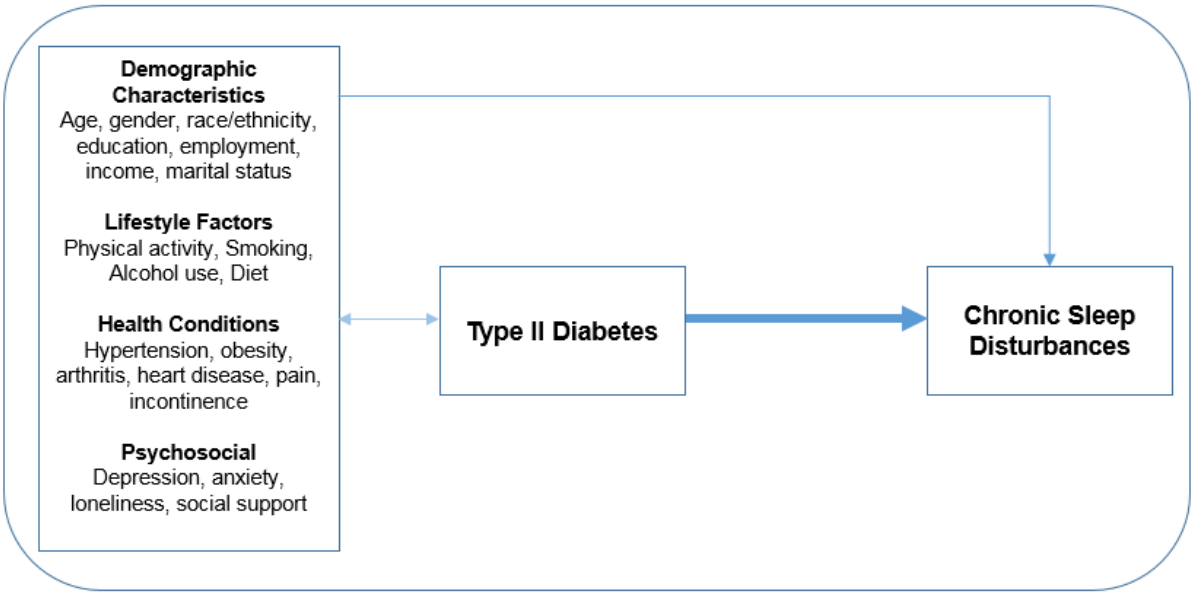
b) Does this association vary by gender?



Aim 2. Determine the association between newly reported diabetes and the development of chronic sleep disturbances.

c) Are those with diabetes at higher risk of developing sleep problems within 4 years than those without diabetes?

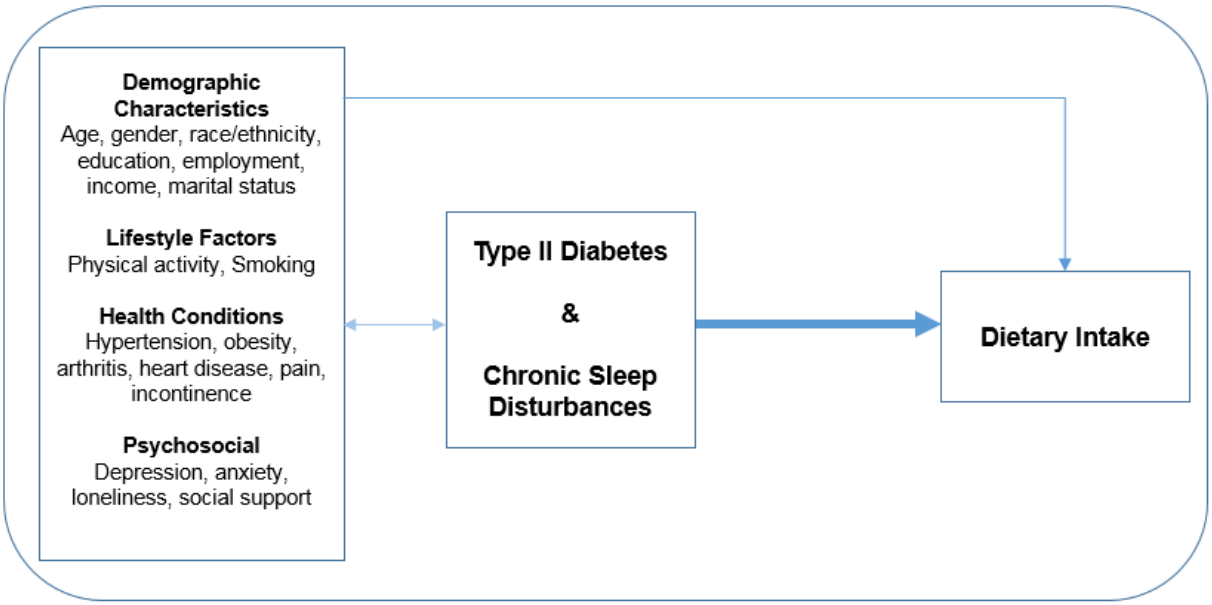
d) Does this association vary by gender?



Aim 3. Determine the association between comorbidity of chronic sleep disturbances and diabetes and the effect on healthy dietary intake, measured by a Mediterranean diet score.

e) Are those with diabetes and chronic sleep disturbances less likely to consume a healthy diet, as measured by a Mediterranean Diet score, than those without sleep problems?

f) Does this association vary by gender?



Public health significance and implications

This dissertation will provide additional information on the risks associated with poor quality sleep. Given that sleep is a basic biological need, and poor quality sleep is a concern over the lifecourse, these findings will help to inform the public health discourse on the potentially deleterious effects of chronic sleep disturbances. In doing so, a focus on the necessity of quality sleep and ensuring that the conditions necessary for high quality sleep (i.e. sleep hygiene) can then be addressed. More specifically, the results of this dissertation will further our knowledge of the chronic sleep disturbances and the multi-directional association with type II diabetes. In doing so, this dissertation will provide additional evidence to support the role of sleep as a critical measure of health that should be assessed among those with, and those at risk of developing, type II diabetes. Doing so can potentially improve quality of life and decrease the costs and burden associated with the comorbidity of chronic conditions.

Currently, the American Diabetes Association recommendations for those recently diagnosed with diabetes include guidance on dietary intake, physical activity, alcohol and smoking, weight loss, support and medication but not on the importance of maintaining sleep quality (73). Training among physicians on the importance of healthy sleep is rarely covered in medical school (74). However, given our increased knowledge of the deleterious effects of poor quality sleep and chronic sleep disturbances, prevention, detection and treatment should be emphasized.

As we turn to new frontiers in health care, led by the move towards individualized medicine, the need to examine subgroups of populations is of greater importance. It is necessary to determine the subgroups of populations at increased risk for the development and progression of disease. This dissertation will attempt to determine differences in the association between

chronic sleep disturbances and diabetes by gender, as well as by race and ethnicity where possible. One of the hallmarks of an aging population is the increase in chronic conditions, such as diabetes, hypertension, arthritis, and the comorbidity of such conditions (75-76). While mortality rates due to infectious diseases and childbirth have declined, women are now at greater risk for comorbid chronic conditions later in life than ever before. Identifying modifiable risk factors, such as chronic sleep disturbances, allows for the prevention, detection and intervention to reduce the unnecessary burden associated with comorbidity of chronic conditions. Identification of such risk factors is becoming ever more important in an aging, diverse society. As with other chronic conditions, prevention as well as early detection of insufficient quality sleep, or chronic sleep disturbances, is necessary in order to provide the necessary treatment and decrease the risk of poor physical and mental health effects that can ensue from chronic sleep disturbances.

References

1. International Diabetes Federation (IDF) Diabetes Atlas. (2010). Prevalence estimates of diabetes mellitus (DM), 2010. Brussels, Belgium.

2. Scott SK, Harris RE. Epidemiology of diabetes mellitus. In Epidemiology of Chronic Disease: Global Perspectives. Jones & Bartlett Learning, LLC, 2013. p.3 75-416.

3. Geiss L, Wang J, Cheng Y, Thompson T, Barker L, Li Y, Albright A, Gregg E. Prevalence and Incidence Trends for Diagnosed Diabetes Among Adults Aged 20 to 79 Years, United States, 1980-2012. JAMA. 2014;312(12):1218-1226.

4. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053.

5. Narayan KMV, Boyle J, Thompson T, et al. Lifetime risk for diabetes mellitus in the United States. JAMA 2003; 290(14):1884-1890. doi 10.1001/jama290.14.1884.

6. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013;36(4):1033-46.

7. The Staggering Costs of Diabetes; 2015. Available from diabetes.org/advocacy/news-events/cost-of-diabetes.html. Accessed 9 Nov 2017.

8. Cappuccio F, Miller M, Lockley S. Sleep, Health, and Society: From Aetiology to Public Health. 2010. New York. Oxford University Press.

9. Kawakami N, Takatsuka N, Shimizu H. Sleep disturbance and onset of type 2 diabetes. Diabetes Care 2004;27:282-283.

10. Meisinger C, Heier M, Loewel H. MONICA/KORA Augsburg Cohort Study. Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population. Diabetologia 2005;48:235-241.

11. Ford E, Wheaton A, Chapman D, Li C, Perry G, Croft J. Associations between self-reported sleep duration and sleeping disorder with concentrations of fasting and 2-h glucose, insulin, and glycosylated hemoglobin among adults without diagnosed diabetes. J Diabetes. 2014;6(4):338-350.

12. Knutson KL, Wu D, Patel S, Loredo J, Redline S, Cai J, Gallo L, Mossavar-Rahmani Y, Ramos A, Teng Y, Daviglus M, Zee P. Association between sleep timing, obesity, diabetes: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Cohort Study. Sleep. 2017. 40.4:1-8.

13. Beihl D, Liese A, Haffner S. Sleep Duration as a Risk Factor for Incident Type 2 Diabetes in a Multiethnic Cohort. Annals of Epidemiology. 2009;19.5:351-357.

14. Zizi F, Pandey A, Murrray-Bachmann R, Vincent M, McFarlane S, Ogedegbe G, Girardin JL, Race/ethnicity, sleep duration, and diabetes mellitus: analysis of the National Health Interview Survey. The American Journal of Medicine. 2012;125: 2. 162-167.

15. Ayas N, White D, Al-Delaimy W, Manson J, Stampfer M, Speizer F, Patel S, Hu F. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care. 2003. 26:2,380-384.

16. Gangwish J, Heymsfield S, Boden-Albala B, Bujis R, Kreier F, Pickering T, Rundle A, Zammit G, Malaspina D. Sleep duration as a risk factor for diabetes incidence in a large US sample. Sleep. 2007. 20:12,1667-1673.

17. Schan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson C, Hu F, Liu L. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care. 2015. 38(3):529-37.

18. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33:414-420.

19. Zhilei S, Mongfel M, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson C, Hu F, Liu L. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies.

20. Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. Diabetes Care 2005;28:2762-2767.

21. Broussard J, Knutson KL. Sleep and metabolic disease. In Sleep, Health, and Society: From Aetiology to Public Health. Cappuccio F, Miller M, Lockley S. New York, Oxford University Press. 2010, p. 111-140.

22. Lockley SW. Principles of sleep-wake regulation. In Sleep, Health, and Society: From Aetiology to Public Health. Cappuccio F, Miller M, Lockley S. New York, Oxford University Press. 2010, p. 9-24.

23. Ferrie JE, Kumari M, Salo P, Singh-Manoux A, Kivimaki M. Sleep epidemiology- a rapidly growing field. International Journal of Epidemiology. 2011.(40):1431-1437.

24. Ohayon M, Wickwire EM, Hirshkowitz M, Albert SM, Avidan A, Daly FJ, et al. National Sleep Foundation's sleep quality recommendations: first report. Sleep Health. 2017.(3):6-19.

25. Perry GS, Pail SP, Presley-Cantrell LR. Raising awareness of sleep as a healthy behavior. Prev Chron Dis. 2013. 10:130081. DOI: http://dx.doi.org/10.5888/pcd10.130081.

26. What happens when you sleep [article online], 2016. Available from https://sleepfoundation.org/how-sleep-works/what-happens-when-you-sleep. Accessed 26 Oct 2016.

27. Spiegel K, Leproult R, VanCauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999. 354;1435-1439.

28. Garcia G, Freeman R, Supiano M, Smith M, Galecki A, Halter J. Glucose metabolism in older adults: a study including subjects more than 80 years of age. J Am Geriatr Soc. 1997. 45;813-817.

29. Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. Diabetes. 2002. 51;(S1):S212-S220.

30. Spiegel K, Leproult R, L'Hermite-Baleriaux M, Copinschi G, Penev P, VanCauter E. Leptin levels are dependent on sleep duration: Relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. Journal of Clinical Endocrinology and Metabolism. 2004. 89;5762-5771.

31. Spiegel K, Tasali E, Penev P, VanCauter E. Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels and increased hunger and appetite. Annals of Internal Medicine. 2004. 141;846-850.

32. Chin-Chance C. Polonsky KS, Schoeller D. Twenty-four hour leptin levels respond to cumulative short-term energy imbalance and predict subsequent intake. Journal of Clinical Endocrinology and Metabolism. 2000. 85;2685-2691.

33. Guilleminault C, Powell NB, Martinez S, et al. Preliminary observations on the effects of sleep in a sleep-restriction paradigm. Sleep Medicine. 2003. 4;177-184.

34. Tasali E, Broussard J, Day A, Kilkus J, VanCauter E. Sleep curtailment in healthy young adults is associated with increased ad lib food intake. Sleep. 2009. 32;A131.

35. Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snack. American Journal of Clinical Nutrition. 2009. 89;126-133.

36. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance and inflammatory cytokines. Journal of Clinical Endocrinology and Metabolism. 2004.89;2119-2126.

37. Hoevenaar-Blom M, Spijkerman A, Kromhout D, van den Berg J, Verschuren M. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. Sleep 2011; 34.11:1487-1492.

38. Johnson DA, Lisabeth L, Lewis T, Sims M, Hickson D, Samdarshi T, Taylor H, Diez-Roux A. The contribution of psychosocial stressors to sleep among African Americans in the Jackson Heart Study. Sleep 2016;39.7:1411-1419.

39. Chen X, Wang R, Zee P, Lutsey P, Javaheri S, Alcantara C, Jackson C, Williams M, Redline S. Racial/ethnic differences in sleep disturbances: the Multi-Ethnic Study of Atherosclerosis (MESA). Sleep. 2015. 38:6, 877-880.

40. Grandner MA, Hale L, Jackson N, et al. Perceived Racial Discrimination as an Independent Predictor of Sleep Disturbance and Daytime Fatigue. Behav Sleep Med. 2012; 10(4):235-249.

41. Hale L, Hill T, Friedman E, et al. Perceived neighborhood quality, sleep quality, and health status: Evidence from the Survey of the Health of Wisconsin. Soc Sci and Med. 2013. 79:16-22.

42. Patel N, Grandner M, Gooneratne N, et al. "Sleep disparity" in the population: poor sleep quality is strongly associated with poverty and ethnicity. BMC Public Health.2010; 10:475-487.

43. Patel S, Sotres-Alvarez D, Castaneda S, Dudley K, Gallo L, Hernandez R, Medeiros E, Penedo F,

Mossavar-Rahmain Y, Ramos A, Redline S, Reid K, Zee P. Social and health correlates of sleep duration in a US Hispanic population: results for the Hispanic Community Health Study/Study of Latinos. Sleep. 2015. 38:10,1515-1522.

44. Loredo J, Soler X, Bardwell W, Ancoli-Israel S, Dimsdale J, Palinkas L. Sleep health in U.S. Hispanic population. Sleep. 2010. 33:7,962-967.

45. Knutson KL, Ryden AM, Mander BA, VanCauter E. Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. Archives of Internal Medicine. 2006. 166:1768-1774.

46. Cespedes EM, Dudley KA, Sotres-Alvarez D, Zee PC, Daviglus ML, Shah NA, et al. Joint associations of insomnia and sleep duration with prevalent diabetes: The Hispanic Community Health Study/Study of Latinos. Journal of Diabetes. 2016. 8(3):387-397.

47. Ohkuma T, Fuji H, Iwase M, Kikuchi Y, Ogata S, Idewaki Y, et al. Impact of sleep duration on obesity and the glycemic level in patients with type 2 diabetes: The Fukoka Diabetes Registry. Diabetes Care. 2013. 36:611-617.

48. Kim BK, Kim BS, An SY, Lee MS, Choi YJ, Han SJ, et al. Sleep duration and glycemic control in patients with diabetes mellitus: Korea National Health and Nutrition Examination Survey 2007-2010. Journal of Korean Medical Sciences. 2013. 28;1334-1339.

49. Samieri C, Sun Q, Townsend M et al. The relation of midlife diet to healthy aging: a cohort study. Annals of Internal Medicine. 2013. 159(9):584-591.

50. De Koning L, Chiuve S, Fung T, et al. Diet-quality scores and the risk of type 2 diabetes in men. Diabetes Care. 2011. 34(1150-1156).

51. Casas-Agustench P, Lopez-Uriarte P, Bullo M, Ros E, Cabre-Vila J, Salas-Salvado J. Effects on one serving of mixed nuts on serum lipids, insulin resistance and inflammatory markers in patients with the metabolic syndrome. Nutrition, Metabolism and Cardiovascular Diseases. 2011. 21:126-135;

52. Guasch-Ferre M, Becerra-Tomas N, Ruiz-Canela M, et al. Total and subtypes of dietary fat intake and risk of type 2 diabetes mellitus in the prevencion con dieta Meditarranea (PREDIMED) study. American Journal of Clinical Nutrition. 2017. 105:723-35.

53. Santangelo C, Filesi C, Vari R, et al. Consumption of extra-virgin olive oil rich in phenolic compounds improves metabolic control in patients with type 2 diabetes mellitus: a possible involvement of reduced levels of circulating visfatin. Journal of Endocrinology Investigation. 2016. 39:1295-1301.

54. Jacobs S, Boushey C, Franke A, et al. A priori-defined diet quality indices, biomarkers and risk for type 2 diabetes in five ethnic groups: the Multiethnic Cohort. British Journal of Nutrition. 2017. 118:312-320.

55. Kang I, Buckner T, Shay NF, Gu L, Chung S. Improvements in metabolic health with consumption of ellagic acid and subsequent conversion into urolithins: evidence and mechanisms. Advances in Nutrition. 2016. 15;7(5):961-72.

56. Guasch-Ferre M, Merino J, Sun Q. Dietary polyphenols, Mediterranean diet, prediabetes, and type 2 diabetes: a narrative review of the evidence. Oxidative Medicine and Cellular Longevity. 2017. 1-16.

57. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. New England Journal of Medicine. 2003;348(26):2599-608.

58. Trichopolou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. British Medical Journal. 1995. 311(7018):1457-60.

59. Willett W, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, and Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. American Journal of Clinical Nutrition. 1995. 61:1402S-1406S.

60. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: A Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutrition, Metabolism and Cardiovascular Diseases. 2006. 16(8); 559-568.

61. Samieri C, Sun Q, Townsend M et al. The relation of midlife diet to healthy aging: a cohort study. Annals of Internal Medicine. 2013. 159(9):584-591.

62. DeKoning L, Chiuve S, Fung T, et al. Diet-quality scores and the risk of type 2 diabetes in men. Diabetes Care. 2011. 34(1150-1156).

63. Campanini M, Guallar Castillon P, Rodriguez-Artalejo F, Lopez-Garcia E. Mediterranean diet and changes in sleep duration and indicators of sleep quality in older adults. Sleep. 2017. 40(3):1-9.

64. Sofi F, Macchi C, Abbate R, Gensini F, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr. 2014 Dec;17(12):2769-82.

65. Herrera MC, Subhan F, Chan C. Dietary patterns and cardiovascular disease risk in people with type 2 diabetes. Current Obesity Reports. 2017 Oct 23. doi: 10.1007/s13679-017-0284-5.

66. Diez-Espino J, Buil-Cosiales P, Serrano-Martinez M, et al. Adherence to the Mediterranean diet in patients with type 2 diabetes mellitus and HbA1c level. Annals of Nutrition and Metabolism. 2011. 58:74-78.

67. Sonnega A, Faul JD, Ofstedal MB et al. Cohort profile: The Health and Retirement Study (HRS). International Journal of Epidemiology. 2014. 43:576-585.

68. Heeringa SG, Connor J. Technical Description of the Health and Retirement Study Sample Design. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 1995.

69. Health and Retirement Study, Cross-wave Tracker, 2006-2014 Core public use dataset, Biomarker data, Health Care and Nutrition Survey 2013. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI, (2017).

70. Crimmins EM, Guyer H, Langa KM, Ofstedal MB, Wallace RB, Weir DR. Documentation of

Physical Measures, Anthropometrics and Blood Pressure in the Health and Retirement Study. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 2008.

71. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantative food frequency questionnaire. American Journal of Epidemiology. 1985. 122(1):51-65.

72. Willett, W. Nutritional Epidemiology. 3. New York and Oxford: Oxford University Press; 2012.

73. Living with diabetes: Recently diagnosed. American Diabetes Association. http://www.diabetes.org/living-with-diabetes/recently-diagnosed. Accessed 7 Nov 17.

74. Cappuccio FP, Miller MA, Lockley SW. Sleep, health, and society: the contribution of epidemiology. In Sleep, Health, and Society: From Aetiology to Public Health. Cappuccio F, Miller M, Lockley S. New York, Oxford University Press. 2010, p. 1-8.

75. Percent of U.S. Adults 55 and Over with Chronic Conditions. Centers for Disease Control. National Center for Health Statistics. Sept 2009. https://www.cdc.gov/nchs/health_policy/adult_chronic_conditions.htm. Accessed 7 Nov 2017.

76. Ward BW, Schiller JS, Goodman RA. Multiple chronic conditions among US adults: a 2012 update. Prevention of Chronic Disease. 2014. 11:E62.

Chapter 2 Chronic Sleep Disturbances are Associated with Incident Diabetes in Older Adults: Variations by Gender and Race/Ethnicity

Abstract

Study Objectives: The current study was conducted to determine whether self-reported chronic sleep disturbances are predictive of incident diabetes in older adults, as well as to determine variations by gender and race/ethnicity.

Methods: 7446 participants from the Health and Retirement Study, a nationally-representative longitudinal cohort study of U.S. adults, were followed for eight years, between 2006 and 2014. Chronic sleep disturbance was defined as self-reported trouble falling asleep or staying asleep "most of the time". Diabetes was based on self-reported doctor's diagnosis or a Hemoglobin A1C value >=6.5mg/dl. Hazard ratios were calculated for baseline and on-going sleep disturbances.

Results: The average age of participants was 63.5 years. Close to 30% of men and 40% of women reported having a chronic sleep disturbance at baseline. The cumulative incidence over the eight year study period of diabetes was 17.7% among men and 15.2% among women. Both men and women who developed diabetes were more likely to report chronic sleep disturbances at baseline than those who did not develop diabetes (Men: 32.2% vs 27.3%; Women: 44.2% vs 36.0%). Women were more likely to develop diabetes within eight years than men after adjustment for demographic covariates (Women: HR 1.40 95% CI 1.19-1.63; Men HR 1.27 95%

CI 0.98-1.66). Black and Hispanic men and women with chronic sleep disturbances had a greater likelihood of developing diabetes within eight years than white men and women.

Conclusions: Self-reported chronic sleep disturbance is an independent predictor of incident diabetes in women. The likelihood of developing diabetes among those with chronic sleep disturbances is greater for women than men and greater for Blacks and Hispanics than non-Black/Hispanic older adults. This finding has both public health and clinical relevance in an aging society.

Key words: sleep quality, sleep disturbance, gender, incident diabetes, hazards ratio, aging, cohort study

Statement of Significance

This longitudinal, population-based study is one of the first in the U.S. to demonstrate the increased hazard of developing diabetes associated with chronic sleep disturbances in Black and Hispanic women. Previous studies have primarily focused on sleep duration rather than sleep quality and on non-Hispanic/non-Black populations. The methods and findings of this study allow for the detection of a robust association between chronic sleep disturbances and incident diabetes taking into account changes in risk factors over time. Future studies should further explore gender-based differences over time as well as among younger adults of Black and Hispanic descent. The public health and clinical implications of sleep disturbances must be acknowledged at the population level as well as individual level in an aging society with rapid increases in the prevalence of both sleep disturbances and diabetes.

Introduction

Sleep disturbances are gaining increasing attention as a primary cause, or contributor, in the development and progression of chronic diseases (1-11). Sleep disturbances may include insomnia, a sleep disorder characterized by either the inability to fall asleep or difficulty staying asleep (i.e. broken sleep), as well as those related to medical conditions such as sleep apnea, restless leg syndrome and nocturia (12). The global burden of poor sleep is increasing, with women typically reporting higher levels of sleep disturbance and poor quality sleep than men (13). It is estimated that over 40 million American workers, approximately 30% of the work force, do not get sufficient sleep on a regular basis (13) and recent Centers for Disease Control (CDC) data shows that over nine million Americans take prescription sleeping aides on a daily basis (14). In an attempt to address the high levels of sleep disturbances in the United States, the CDC included a goal in the Healthy People 2020 objectives to increase the rate of sufficient

sleep among adults to seven hours or more per 24-hour period (15-16). Disparities in sleep duration and sleep quality have been identified for women, compared to men, and among Black adults compared to white and Hispanic adults (17-23).

Public health concerns related to poor quality sleep are multi-factorial and include not only the development of chronic diseases, but also lost days of work, decreased quality of life and increased medical and prescription costs associated with sleep disturbance. While sleep itself is a basic biological need, poor quality sleep can lead to the inability to fight off infection, perform well in school and work, and metabolize sugar to prevent diabetes. Poor sleep has been linked to multiple diseases and chronic conditions including obesity, diabetes, cardiovascular disease, stroke and even mortality (1-11). The prevalence and incidence of type II diabetes has increased substantially over the past decade and continues to rise worldwide (25-27) with the greatest risk in the U.S. among Black and Hispanic adults (28). Similarly, the increased incidence of diabetes raises the risk of other diabetic complications, lost employment time and wages, increased medical care costs, higher rates of comorbidity with other chronic conditions and mortality (29). Thus, not only is prevention of the onset of Type II diabetes an important public health concern, prevention of the progression of comorbid conditions is important once a diagnosis is received.

Numerous studies, primarily cross-sectional, have examined the association between sleep duration, and to a lesser degree sleep quality, and incident diabetes in adult populations (30-42). Yet, a gap exists in the current literature in the role of poor sleep quality and diabetes among a nationally representative, longitudinal, sample of multi-ethnic older women and men in the United States. Most studies to date are of populations of European/Asian descent and few have sufficient sample sizes of Black or Hispanic populations to report associations among these

subgroups. Given the higher rates of sleep disturbances reported by Black adults and the higher rates of obesity, hypertension and type II diabetes among Black and Hispanic adults, understanding the role of sleep disturbances in the development of diabetes could provide information that has both clinical relevance as well as public health implications. Additionally, most studies assess risk in younger adults whereas the incidence of diabetes increases as adults age. Given the aging population, shifting demographics and the increase in diabetes in the United States, there is a need to examine these associations differentially by gender as well as by race/ethnicity within gender.

In this study, we assessed the longitudinal association between poor sleep quality and incident diabetes. The study addressed two primary questions: 1) Is poor sleep quality associated with incident diabetes within eight years among older home-dwelling adults and, 2) Does this association vary by gender and race/ethnicity? Additionally, the impact of changes over time among known risk factors will be assessed as well.

Methods

Participants

Health and Retirement Study

Participants were drawn from the Health and Retirement Study (HRS). The HRS is a national, longitudinal study representative of the U.S. population aged 51 and older. The study began in 1992 and includes a new cohort of individuals age 50-55 every six years in order to maintain representation of the U.S. population in this age group as well as the older age groups as the study sample ages. Panel participants are interviewed every two years by phone or in person. The complex sample design, including oversamples of Black and Hispanic participants, allows for broad population-based inferences (43-45). The Health and Retirement Study is approved by the University of Michigan Institutional

Review Board (46). The Health and Retirement Study (HRS) is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan.

Study Sample

Participants for the current study were selected from those who completed an HRS interview in 2006. Figure 2.1 provides a description of the sample. A total of 7,446 participants (4668 women, 2778 men) were included in the current study ranging in age from 52-96. These participants were alive through 2014 and completed biannual interviewer-assisted interview between 2006 to 2014. Participants did not have a diagnosis of diabetes at the start of the study. Participants who were interviewed by proxy or resided in a nursing home were not eligible for inclusion in the study.

Measures

Self-reported measures of demographic characteristics and health status were collected at each two-year period.

Exposure: Sleep disturbances

Participants were asked three questions related to sleep disturbance in 2006, 2010 and 2014. The three questions were summed to create the exposure variable to assess chronic sleep disturbances.

Disturbances in sleep quality were assessed based on self-reported frequency of having trouble falling asleep, waking up during the night and waking up too early and not being able to fall back asleep. Responses were dichotomized for each of the three questions to 1=Yes (Most of the time) or 0=No (Sometimes, rarely or never) in order to capture ongoing, chronic sleep disturbances. The number of sleep disturbance problems endorsed was calculated by summing the response to these three questions. A composite variable was created to categorize those who reported that they had one or more sleep problems most of the time.

Outcome: Incident diabetes

Incident diabetes was defined as self-reported diabetes in any wave of follow-up or a hemoglobin A1C (HbA1c) result of 6.5mg/dL or greater, assayed from a non-fasting dried blood spot collected in the home at the time of the interview (28).

Covariates: Demographic, health behaviors, health conditions

Demographic variables included age calculated based on self-reported year of birth, gender, years of education and race/ethnicity. Respondents were categorized as Hispanic, non-Hispanic Black, non-Hispanic White/Other based on responses to two separate questions on Hispanic ethnicity and race. Socio-economic status (SES) at baseline was calculated based on tertiles of total wealth obtained from the HRS-RAND economic data. This measure of total wealth included all income and assets of the respondent and other household members, such as a spouse or partner. Gender-specific tertiles were calculated and participants were categorized as low SES, middle SES and high SES based on the tertile of total wealth. Marital status and employment were asked at each interview. Marital status was coded as currently married versus not married (including never married, separated/divorced and widowed). Work status was coded as currently working or not working. Marital and employment status were considered time-varying covariates.

Health behaviors of interest included self-reported measures of physical activity, current smoking status and current alcohol consumption. Participants who reported engaging in moderate or vigorous physical activity at least once a week on average were considered to be physically active. Respondents who reported that they were current cigarette smokers were categorized as smokers. Current alcohol consumption on two or more days per week was categorized as positive for alcohol consumption. Health behaviors were collected during each interview.

Other health conditions that were potential confounders or moderators in the association between chronic sleep disturbances and incident diabetes were included based on self-report (Has a doctor or other medical professional ever told you that you have…"). Health conditions of interest included hypertension, heart disease, stroke, lung diseases, cancer, emotional, nervous or psychiatric problems (such as depression, anxiety), chronic pain and urinary incontinence. Body mass index (BMI) was calculated based on self-reported height and weight. A BMI of 30 or greater was considered obese. Health conditions were assessed at each biannual interview.

Statistical Analysis

A longitudinal dataset was created with responses from interviews conducted in 2006, 2008, 2010, 2012 and 2014, with 2006 considered the baseline wave for the current analysis. Descriptive data analysis of all baseline characteristics was conducted for all of the sample as well as with the exposure variables as well as the outcome variables. Mean values of continuous variables were compared using t-tests. Rao-Scott chi-square tests were utilized to assess the bivariate associations of categorical variables. All reported values were weighted for survey design and non-response. Survey-specific procedures were used to compute 95% confidence intervals to account for the multi-stage clustered sample design. Differences between those with and without diabetes were estimated using the overall Wald test. The cumulative incidence of diabetes was calculated overall and by gender. Population years of follow-up were used to calculate crude incidence rates by gender and race/ethnicity. A priori knowledge of risk factors for the development of type II diabetes were included as covariates in Cox proportional hazards models. Multiple Cox proportional hazards models were estimated to assess the proportional hazard of developing diabetes among those with chronic sleep disturbances at baseline compared to those without a chronic sleep disturbance. Cox proportional hazards models were stratified by

gender to account for the differences by gender in the exposure and the outcome. A series of six Cox proportional hazards models were estimated to determine the marginal impact of different covariates of interest on the association of the baseline exposure and outcome. The first model was unadjusted to determine the association between the exposure variable, one or more chronic sleep disturbances at baseline, and the development of diabetes over time. Model Adjusted-1 adjusted for age at baseline and race/ethnicity as well as having one or more chronic sleep disturbance at baseline. Model Adjusted-2 adjusted for variables from the previous model as well as socio-economic status. Model Adjusted-3 adjusted for variables from the previous model as well as two health predictors- obesity and hypertension. Model Adjusted-4 adjusted for variables from the previous model as well as health behavior variables- physical activity, alcohol use and smoking status. Model Adjusted-5 adjusted for variables from the previous model as well as other chronic health conditions—heart disease, chronic pain, emotional problems and incontinence—as well as other lifestyle factors (marital and employment status). The seventh model included all of the baseline variables in the previous model as well as time-varying covariates for the follow up years 2008-2014. This seventh Cox proportional hazards model was estimated to adjust for time-varying exposure variables and covariates including biannual changes in chronic sleep disturbances, marital status, employment status, physical activity, alcohol consumption, smoking, hypertension, obesity, heart disease, incontinence, emotional problems and chronic pain. Interaction terms for race/ethnicity and obesity, race/ethnicity and hypertension and race/ethnicity and chronic sleep disturbances were assessed in models 6 and 7. Hazard ratios and 95% confidence intervals were calculated for all covariates in each model (47). The complex sample design characteristics (strata, cluster and respondent weights) were utilized at all stages of analysis (proc surveymean, proc surveyfreq, proc surveyphreg) (48). All

percentages and mean values reported are weighted for the complex sample design. All statistical tests were two-sided at a significance level of .05. SAS v9.4 was used for data analysis.

Results

Close to six-tenths of the study population were female (58.4%) and the average age of all participants was 63.5 (SE 4.9, range 50-96). Just under fifteen percent of the study population were Black or Hispanic (7.7% and 6.4% respectively). Over half of participants had some college or a college degree (54.9%) and over half were working at baseline (51.2%). Over seventy percent of men and women reported engaging in physical activity on a weekly basis. Fourteen percent reported currently smoking and close to one-third of all respondents reported alcohol consumption on two or more days per week (28.6%). Men reported engaging in weekly physical activity, smoking and consuming alcohol more frequently than women. Overall, hypertension was the most prevalent health condition (45.7%) followed by obesity (31.5%), chronic pain (30.5%), heart disease (16.6%) and emotional or psychiatric problems (16.1%). Women were more likely to be hypertensive, report chronic pain and emotional/psychiatric problems than men. Men were more likely to report having heart disease than women (Table 2.1).

Baseline sleep disturbances by gender and race/ethnicity within gender are shown in Table 2.2. Women were more than twice as likely to report having difficulty falling asleep than men. Women were also more likely to report chronic problems with waking up at night and not falling back asleep and waking up too early in the morning and not falling back asleep. Overall, 37.1% of women and 28.2% of men reported one or more chronic sleep problem. A lower proportion of both men and women reported that they rarely or never feel well rested when they wake up in the morning (14.0% men, 17.1% women). All differences between genders were

significant ($p<0.0001$). Among men, white males were more almost twice as likely to report chronic difficulties with waking up at night and not feeling well rested when waking up in the morning compared to Black and Hispanic males. Similar rates of Black and Hispanic men reported one or more chronic sleep problems (21.8% and 22.6%, respectively) while Hispanic men were more likely to report having problems waking up at night whereas Black men were more likely to report similar levels of disturbances waking up at night and waking up too early. Among women, significant differences were observed by race/ethnicity for chronic disturbances waking up at night, waking up too early in the morning and having one or more chronic sleep disturbance. More variation was observed in women than in men by race/ethnicity within each type of disturbance. For example, Hispanic women were more likely than white and Black women to report chronic disturbances falling asleep at night (20.0% vs 14.8% vs 15.1%, respectively). White women were more likely to report chronic disturbances waking up at night than Black or Hispanic women (29.5% vs 20.6% vs 18.4%). Among both men and women, white participants were most likely to report chronic sleep disturbances followed by Hispanic participants with Black participants reporting the lowest rate of chronic sleep disturbances. However, the rate of sleep disturbances was very similar for Hispanic and Black participants overall and both were approximately 25% lower than white men, 20% lower than white women.

The cumulative incidence rate of diabetes within the eight year follow-up period was 15.6%. Table 2.3 shows the baseline characteristics of men and women by diabetic status in 2014. Men were more likely to develop diabetes than women within the eight-year follow-up period (17.7% vs 15.2%). Participants who developed diabetes were more likely to be Black or Hispanic, have a lower education level, not be currently married or working and have lower SES at baseline than those who did not develop diabetes. These results were consistent for men and

women. Both men and women who developed diabetes were less likely to engage in weekly physical activity, more likely to smoke and less likely to consume alcohol on a weekly basis. In terms of chronic health conditions at baseline, participants that developed diabetes were more likely to have each of the chronic conditions assessed than those who did not develop diabetes, with two exceptions—cancer for both genders and emotional problems in women.

Crude incidence rates of diabetes by gender, race/ethnicity and the presence or lack of presence of chronic sleep disturbances at baseline are shown in Table 2.4. Incidence rates were higher in men and women with chronic sleep disturbances compared to those without sleep disturbances at baseline. Black women and men with baseline chronic sleep disturbances had the highest rates of incident diabetes. While Hispanic women with baseline chronic sleep disturbances had the second highest crude incidence rate of diabetes, Hispanic men with and without sleep disturbances had higher rates of incident diabetes. For all subgroups, 8-year crude incidence rates of diabetes were higher among those who reported chronic sleep disturbances than those who did not.

Cox proportional hazards models were calculated separately for men and women given the differences in the association of sleep and diabetes between and within gender. Seven models are shown in tables 2.5 (women) and in table 2.6 (men). In unadjusted models, we found that women with chronic sleep disturbances at baseline had a 37% greater proportional hazard of developing diabetes during the eight-year follow up period than those without diabetes (HR 1.37, 95% CI 1.17-1.60). While men also had an increased likelihood of developing diabetes, the association approached significance but was not statistically significant (HR 1.25; 95% CI 0.96-1.62). The hazard ratio of developing incident diabetes due to chronic sleep disturbances increased in both men and women after adjustment for demographic characteristics (adjusted

models 1 and 2). However, the association was attenuated after adjusting for additional lifestyle factors and chronic conditions (adjusted models 3-5). The greatest reduction in the hazard ratio for sleep disturbances was observed when hypertension and obesity are incorporated in the models. This pattern is consistent for men and women. First order interaction terms among sleep, hypertension and obesity were not significant for men or women.

After adjusting for all other covariates (adjusted model 5), women with one or more chronic sleep disturbance at baseline had a hazard ratio of 1.29 (95% CI 1.11-1.49) of developing diabetes within eight years. Other covariates that were significant predictors of developing diabetes were age, being Black or Hispanic, being obese and having hypertension. Regular alcohol consumption was protective of developing diabetes within eight years among women. In men, after adjusting for all other covariates, those with one or more chronic sleep disturbances at baseline had a hazard ratio of 1.22 (95% CI 0.94-1.57) of developing diabetes within eight years. Thus, in men, the association between chronic sleep disturbances and incident diabetes approached significance after taking time-varying covariates into account. Other covariates that were significant predictors of developing diabetes in men were being Black or Hispanic, low SES, being obese, having hypertension and having heart disease. Regular alcohol consumption and being married appear protective of developing diabetes within eight years among men.

The incorporation of time-varying covariates (sleep disturbances, obesity, high blood pressure, pain, depression, heart disease, physical activity, alcohol consumption, marital status and work status) slightly attenuated the hazard ratio in both men and women, yet the association remained significant in women (Adjusted-Time-Varying). After adjustment for time-varying lifestyle and health conditions, women with chronic sleep disturbances at baseline had a 27% greater hazard of developing diabetes over the eight-year follow up period compared to those

who did not have chronic sleep disturbances at baseline (HR 1.27; 95% CI 1.08-1.50). In men, the association between chronic sleep disturbances at baseline and the development of type II diabetes over the eight year follow-up period was attenuated after accounting for changes in lifestyle factors and health conditions over time (HR 1.14; 95% CI 0.88-1.48). However, the development of new sleep disturbances during the follow-up period were significantly associated with the development of incident diabetes in men, but not in women (Chronic sleep disturbances between 2008-2014- Women HR 1.03, 95% CI 0.81-1.29; Men HR 1.35, 95% CI 1.07-1.71. Data not shown).

Discussion

In this large, nationally-representative sample, we found that older adults with chronic sleep disturbances are more likely to develop diabetes within eight years than those without chronic sleep disturbances even after controlling for key confounders including age, race/ethnicity, socio-economic status, obesity and hypertension. Women reported chronic sleep disturbances more often than men (37.1% vs 28.2%). While the rate of incident diabetes was slightly lower in women than men, 15.2% vs 17.7%, women with chronic sleep disturbances were significantly more likely to develop diabetes within eight years than those who did not have chronic sleep disturbances. Differences by race and ethnicity within gender were detected. White women and men reported higher levels of chronic sleep disturbances compared to Black and Hispanic adults. However, the crude incidence of diabetes among those with chronic sleep disturbances is more than twice the rate in Black women compared to White women, and 75% greater in Hispanic women than non-Hispanic white women. Among men, the crude incidence rate of diabetes is also close to 80% greater in Black and Hispanic men with chronic sleep disturbances compared to white men. This association remains after controlling for multiple

factors as well as changes in risk factors over time. The hazard remains greatest among women. When evaluating race/ethnicity within gender, Hispanic women have the greatest hazard, followed by Black women. Among men, Black men have the greatest hazard followed by Hispanic men. This study shows that chronic sleep disturbances are a risk factor in the development of diabetes, especially among Black and Hispanic adults. Additionally, on-going sleep disturbances remain a significant predictor of incident diabetes in men. Those who develop diabetes within eight years are more likely to be Black or Hispanic, low income, not working, not married and have poorer health condition and health habits than those who do not develop diabetes.

A systematic review by Cappuccio and colleagues (30) found that both sleep duration and sleep quality predict the risk of developing type II diabetes. The review included ten studies and found the greatest risk among those who reported difficulty initiating sleep (RR 1.57; 95% CI 1.25-1.97) and difficulty maintaining sleep (RR 1.84; 95% CI 1.39-2.43). However, the review was unable to report differences in risk by gender nor by race/ethnicity. Many of the studies included were among non-ethnically diverse populations. Half of the studies included only one gender and could not detect differences by gender in the reference population. The other half of the studies did not report results separately by gender. Additionally, the age of the study populations ranged from 19-69 with most studies assessing risk at 40 years of age. Thus, the association among older adults who developed diabetes may not have been detected. Each of the studies included assessed sleep disturbances based on questionnaires and self-report, similar to the current study. The review by Cappuccio and colleagues is useful in highlighting the risk of incident diabetes among adults with chronic sleep disturbances, however differences by

race/ethnicity were outside of the scope of the review and sleep quality in women was only assessed in studies conducted outside of the U.S..

Meisinger and colleagues (34) found that difficulty maintaining sleep was associated with a higher risk of developing type II diabetes among adults age 25-74 with an average follow-up of 7.5 years. In line with our findings, the hazard ratio in women was greater than in men (Women HR 1.98; 95% CI 1.20-3.29; Men HR 1.60; 95% CI 1.05-2.45). However, difficulty initiating sleep was not significantly associated with developing diabetes in men or women. The study population included participants from the MONICA study conducted in Germany, a racially and ethnically homogenous population. Additionally, the crude incidence rates of diabetes in men and women were much lower than those detected in our study population. Hoevenaar-Blom and colleagues (3) found that short sleep duration accompanied by sleep disturbances increased the risk of incident cardiovascular disease after 10-15 years of follow up. However, this study was a population-based study in the Netherlands and was unable to detect or report differences by gender or race/ethnicity.

Numerous studies have reported increased rates of sleep disturbances among Black and Hispanic adults in the U.S. population. Many of these focus on psychosocial stressors and socio-economic conditions associated with sleep disturbances (17--23). To date, studies assessing the relationship between poor sleep quality and diabetes in racially and ethnically diverse populations are few and have been cross-sectional in nature. Thus, the relationship between poor quality sleep and incident diabetes in non-white populations has not been assessed. The Multi-Ethnic Study of Atherosclerosis (MESA) included 2230 participants with an average age of 68.8 (22). Multiple measures of sleep quality were used including polysomnography, actigraphy and a self-reported questionnaire. Chen and colleagues found that Blacks had higher rates of sleep

apnea, short sleep, poor sleep quality and daytime sleepiness than whites. Hispanics had higher odds of sleep apnea and short sleep. Black men and Hispanic women more likely to report poor sleep quality. The odds of poor sleep quality decreased with age in Blacks but increased among Hispanics. While the Chen et al study concludes that Blacks and Hispanics may be at an increased risk for the development of chronic conditions related to poor sleep, this cross-sectional study did not report on the association between chronic conditions and sleep disturbances.

Previous studies have focused primarily on the association between sleep duration and diabetes. These studies have found a positive association between both short sleep duration and long sleep duration with the onset of diabetes, as well as short sleep duration accompanied by sleep disruption. Using data from the National Health Interview Survey, a cross-sectional population-based study, Zizi and colleagues found that both Black and White participants reporting either short sleep duration, less than 6 hours, or long sleep duration, greater than 8 hours, were at an increased odds of having diabetes than those who slept 6-8 hours per night (38). The association was greater for Blacks than whites. A study by Beihl and colleagues showed that short sleep duration (7 hours or less) was a risk factor for incident diabetes in Hispanics and Whites, but not in Blacks, after five years of follow-up (37). Vgontzas and colleagues invited participants with self-reported insomnia lasting a year or more, or poor quality sleep, to a sleep laboratory to determine the joint effect of an objective measure of short sleep duration and insomnia (10). They found that participants were at a greater risk of diabetes if they had chronic insomnia combined with short sleep duration, 5 hours of sleep a night or less. Poor sleep alone was not associated with diabetes. Knutson and colleagues found that Hispanic adults with delayed sleep timing were at an increased risk of incident diabetes compared to those who

reported earlier bedtimes (36). Of the few longitudinal studies on the effects of sleep quality, the health outcomes of interest have varied including cardiovascular disease, hypertension, obesity, diabetes and quality of life. A longitudinal study conducted by Grossman and colleagues with older adults in Europe found a positive association between persistent sleep problems over six years of follow up and lower quality of life as well as decreased ability to conduct activities of daily living (11).

The current study has several strengths that should be noted. The results are based on a large population-based cohort that has employed a complex sample design allowing for both population-based inferences and subgroup analyses. This has allowed us to detect differences in the association between diabetes and chronic sleep disturbances by gender. Additionally, the outcome of incident diabetes included both those with undetected diabetes as well as self-reported diabetes. Over 30% of those with incident diabetes were categorized as such based on their HbA1C value rather than self-report of a diagnosis. While the detection via A1C rather than self-report varied slightly by race/ethnicity (24% of Hispanic diabetics, 37.5% of Black diabetics and 32.9% of white diabetics), the overall association did not change significantly when the analysis were restricted to those who self-reported a diagnosis of diabetes. Previous studies have assessed difficulty initiating sleep and difficulty maintaining sleep separately whereas we have grouped these disturbances together in the current study. If these sleep quality disturbances have different effects on the development of diabetes, as shown by Meisinger et al (34), the effect of sleep disturbances on incident diabetes may be underestimated in our study. However, a separate analysis not included in this paper, found that the results were not changed when assessing these measures as separate exposures.

Our study has potential limitations. Both the exposure, chronic sleep disturbances, and the outcome, incident diabetes, were based on self-report and could lead to measurement error. Additionally, the exposure was subjective and it was not possible to validate self-reported sleep quality with an objective measure of sleep such as polysomnography or actigraphy. Previous studies have found that men tend to under-report sleep disturbances. Given the difference in sleep disturbance rates among men and women, it is possible that the men in our study population underreported chronic sleep disturbances. This may have contributed to our inability to detect a significant relationship between sleep disorders and incident diabetes among men despite the indication that one exists. Our study is based on interview data and did not include measures, either self-report or objective measures, of sleep apnea, snoring, or family history of diabetes. Thus, it is possible that self-reported chronic sleep disturbances could be proxy measures of sleep apnea. It is possible that confounding due to unmeasured risk factors occurred in our study results. Our study is based on complete case analysis among an older adult population over eight years of follow-up. If the reason for nonresponse or death was related to either the exposure or the outcome, our results may show an attenuated association between the exposure and outcome. Given the age range at baseline of our study participants, mortality could be a competing risk.

In conclusion, our study provides evidence of a robust independent relationship between chronic sleep disturbances and the development of diabetes in older adults, and that the hazard is greater among women and Black and Hispanic adults. In women, sleep disturbances at baseline are predictive of incident diabetes within eight years whereas among men, variations in sleep disturbances over time are more predictive. Future studies should be undertaken to replicate our results with larger populations of racially and ethnically diverse adults. Psychosocial factors

associated with poor quality sleep in these populations should be taken into account as well as determining the age at which risk begins to increase. The findings of this study have both clinical and public health significance in a diverse and aging society.

References

1. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. Nature and Science of Sleep;2017:9 151–161.

2. Chandola T, Ferrie J, Perski Aleksander, Akbaraly T, Marmot M. The effect of short sleep duration on coronary heart disease risk is greatest among those with sleep disturbance: a prospective study from the Whitehall II cohort. Sleep 2010; 33.6:739-744.

3. Hoevenaar-Blom M, Spijkerman A, Kromhout D, van den Berg J, Verschuren M. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. Sleep 2011; 34.11:1487-1492.

4. Narisawa H, Komada Y, Miwa T, Shikuma J, Sakurai M, Odawara M, Inoue Y. Prevalence, symptomatic features, and factors associated with sleep disturbance/insomnia in Japanese patients with type-2 diabetes. Neuropsychiatric Disease and Treatment 2017;13:1873-1880.

5. McNeil J, Doucet E, Chaput JP. Inadequate Sleep as a Contributor to Obesity and Type 2 Diabetes. Can J Diabetes. 2013; 37:103-108.

6. Mahmood W, Yusoff M, Behan L, et al. Association between Sleep Disruption and Levels of Lipids in Causcasians with Type 2 Diabetes. Int J of Endocrinology. 2013;1-7.

7. Petrov ME, Kim Y, Lauderdale D, et al. Longitudinal Associations between Objective Sleep and Lipids: The CARDIA Study. Sleep. 2013;36(11):1587-95.

8. Grandner MA, Chakravorty S, Perlis ML, et al. Habitual sleep duration associated with self-reported and objectively determined cardiometabolic risk factors. Sleep Medicine. 2014:15:42-50.

9. Mesas A, Guallar-Castillon P, Lopez-Garcia E, et al. Sleep quality and the metabolic syndrome: the role of sleep duration and lifestyle. Diabetes Metab Res Rev. 2013;doi: 10.1002.dmrr.2480.

10. Vgontzas A, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler E. Insomnia with objective short sleep duration is associated with type 2 diabetes. Diabetes Care 2009 Nov; 32(11):1980-1985.

11. Grossman ES, Shrira A, Bodner E. Enduring sleep complaints predict health problems: a six-year follow-up of the Survey of Health and Retirement in Europe. Aging and Mental Health, 2016.

12. Krystal A, Edinger J. Measuring Sleep Quality. Sleep Medicine. 9 Suppl. 1 (2008) S10–S17.

13. Centers for Disease Control and Prevention. Insufficient sleep is a public health epidemic. http://www.cdc.gov/Features/dsSleep/. Published March 14, 2013.

14. NCHS Data Brief, Centers for Disease Control and Prevention. Prescription Sleep Aid Use Among Adults: United States, 2005-2010. http://www.cdc.gov/nchs/data/databriefs/db127.pdf. Published August 2013.

15. https://www.healthypeople.gov/2020/topics-objectives/topic/sleep-health/objectives.

16. Ohayon M, Wickwire EM, Hirshkowitz M, Albert SA, Avidan A, Daly FJ, Dauvilliers Y, Ferri R, Fung C, Gozal D, Hazen N, Krystal A, Lichstein K, Mallampalli M, Plazzi G, Rawding R, Scheer FA, Somers V, Vitiello MV. National Sleep Foundation's sleep quality recommendations: first report. Sleep Health 2017;Volume 3.1: 6-19.

17. Johnson DA, Lisabeth L, Lewis T, Sims M, Hickson D, Samdarshi T, Taylor H, Diez-Roux A. The contribution of psychosocial stressors to sleep among African Americans in the Jackson Heart Study. Sleep 2016;39.7:1411-1419.

18. Grandner MA, Hale L, Jackson N, et al. Perceived Racial Discrimination as an Independent Predictor of Sleep Disturbance and Daytime Fatigue. Behav Sleep Med. 2012; 10(4):235-249.

19. Hale L, Hill T, Friedman E, et al. Perceived neighborhood quality, sleep quality, and health status: Evidence from the Survey of the Health of Wisconsin. Soc Sci and Med. 2013. 79:16-22.

20. Patel N, Grandner M, Gooneratne N, et al. “Sleep disparity” in the population: poor sleep quality is strongly associated with poverty and ethnicity. BMC Public Health.2010; 10:475-487.

21. Patel S, Sotres-Alvarez D, Castaneda S, Dudley K, Gallo L, Hernandez R, Medeiros E, Penedo F, Mossavar-Rahmain Y, Ramos A, Redline S, Reid K, Zee P. Social and health correlates of sleep duration in a US Hispanic population: results for the Hispanic Community Health Study/Study of Latinos. Sleep. 2015. 38:10,1515-1522.

22. Chen X, Wang R, Zee P, Lutsey P, Javaheri S, Alcantara C, Jackson C, Williams M, Redline S. Racial/ethnic differences in sleep disturbances: the Multi-Ethnic Study of Atherosclerosis (MESA). Sleep. 2015. 38:6, 877-880.

23. Loredo J, Soler X, Bardwell W, Ancoli-Israel S, Dimsdale J, Palinkas L. Sleep health in U.S. Hispanic population. Sleep. 2010. 33:7,962-967.

24. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium, International Diabetes Federation, 2013.

25. 250.00 diabetes mellitus type 2 (NIDDM, noninsulin-dependent or unspecified). Incidence and Prevalence Data. 2012:0. http://search.proquest.com.proxy.lib.umich.edu/docview/924451600?accountid=14667.

26. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053.

27. Narayan KMV, Boyle J, Thompson T, et al. Lifetime risk for diabetes mellitus in the United States. JAMA 2003; 290(14):1884-1890. doi 10.1001/jama290.14.1884.

28. Geiss L, Wang J, Cheng Y, Thompson T, Barker L, Li Y, Albright A, Gregg E. Prevalence and Incidence Trends for Diagnosed Diabetes Among Adults Aged 20 to 79 Years, United States, 1980-2012. JAMA. 2014;312(12):1218-1226.

29. Epidemiology of Chronic Disease, Global Perspectives. Harris, RE. Jones & Bartlett Learning, LLC. 2013.

30. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33:414-420.

31. Zhilei S, Mongfel M, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson C, Hu F, Liu L. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies.

32. Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. Diabetes Care 2005;28:2762-2767.

33. Kawakami N, Takatsuka N, Shimizu H. Sleep disturbance and onset of type 2 diabetes. Diabetes Care 2004;27:282-283.

34. Meisinger C, Heier M, Loewel H. MONICA/KORA Augsburg Cohort Study. Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population. Diabetologia 2005;48:235-241.

35. Ford E, Wheaton A, Chapman D, Li C, Perry G, Croft J. Associations between self-reported sleep duration and sleeping disorder with concentrations of fasting and 2-h glucose, insulin, and glycosylated hemoglobin among adults without diagnosed diabetes. J Diabetes. 2014;6(4):338-350.

36. Knutson KL, Wu D, Patel S, Loredo J, Redline S, Cai J, Gallo L, Mossavar-Rahmani Y, Ramos A, Teng Y, Daviglus M, Zee P. Association between sleep timing, obesity, diabetes: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Cohort Study. Sleep. 2017. 40.4:1-8.

37. Beihl D, Liese A, Haffner S. Sleep Duration as a Risk Factor for Incident Type 2 Diabetes in a Multiethnic Cohort. Annals of Epidemiology. 2009;19.5:351-357.

38. Zizi F, Pandey A, Murrray-Bachmann R, Vincent M, McFarlane S, Ogedegbe G, Girardin JL, Race/ethnicity, sleep duration, and diabetes mellitus: analysis of the National Health Interview Survey. The American Journal of Medicine. 2012;125: 2. 162-167.

39. Ayas N, White D, Al-Delaimy W, Manson J, Stampfer M, Speizer F, Patel S, Hu F. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care. 2003. 26:2,380-384.

40. Gangwish J, Heymsfield S, Boden-Albala B, Bujis R, Kreier F, Pickering T, Rundle A, Zammit G, Malaspina D. Sleep duration as a risk factor for diabetes incidence in a large US sample. Sleep. 2007. 20:12,1667-1673.

41. Schan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson C, Hu F, Liu L. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care. 2015. 38(3):529-37.

42. Meisinger C, Heier M, Loewel H. Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population. Diabetologia. 2005. 48:235-241.

43. Health and Retirement Study, Cross-wave Tracker, 2006-2014 Core public use dataset. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI, (2017).

44. Health and Retirement Study, Biomarker data, 2006-2012 sensitive health restricted use dataset. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI, (2017).

45. RAND HRS Data, Version P. Produced by the RAND Center for the Study of Aging, with funding from the National Institute on Aging and the Social Security Administration. Santa Monica, CA (August 2016).

46. Heeringa SG, Connor J. Technical Description of the Health and Retirement Study Sample Design. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 1995.

47. Singer J, Willett J. Applied longitudinal data analysis: modeling change and even occurrence. 2003. Oxford University Press, Inc.

48. Heeringa S, West B, Berglund P. Applied survey data analysis; second edition. 2017. CRC Press, Taylor & Francis Group, LLC.

49. Knutson KL. Sociodemographic and cultural determinants of sleep deficiency: Implications for cardiometabolic disease risk. Social Science & Medicine.2013;79:7-15.

Figure 2.1 Study population.

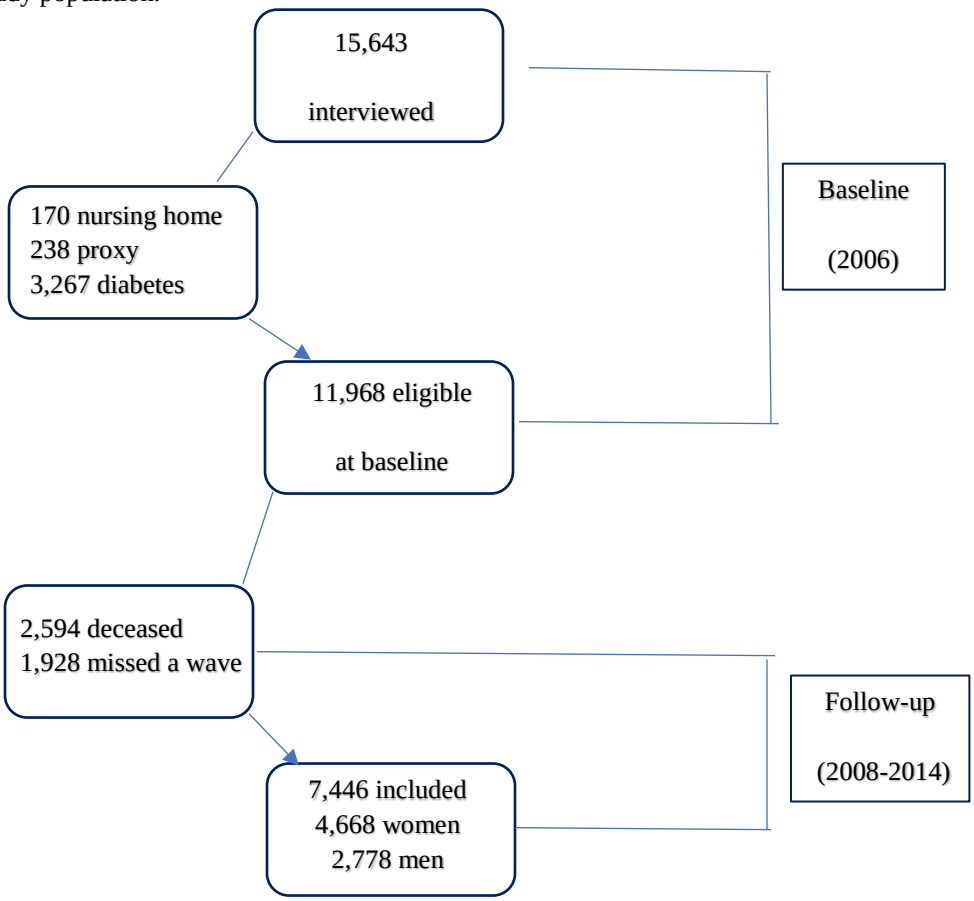


Table 2.1. Baseline characteristics of the study population (weighted)

	Men n=2,778 (41.6%)	Women n=4,668 (58.4%)	All n=7,446 (100%)
Demographic Characteristics	% (SE)	% (SE)	% (SE)
Age (mean yrs, SE)	62.9 (4.9)	63.9 (5.3)	63.5 (4.9)
Race/Ethnicity			
White/other, non-Hisp	87.1 (1.0)	84.9 (1.1)	85.8 (0.9)
Black, non-Hisp	6.8 (0.6)	8.4 (0.6)	7.7 (0.5)
Hispanic	6.1 (0.8)	6.7 (1.0)	6.4 (0.8)
Education (mean yrs, SE)	13.9 (0.1)	13.3 (0.1)	13.6 (0.1)
HS degree or less	39.5 (1.3)	49.1 (1.1)	45.1 (1.0)
Some college or degree	60.5 (1.3)	50.9 (1.1)	54.9 (1.0)
Currently married	74.5 (1.2)	61.4 (0.9)	66.8 (0.8)
Currently working	58.5 (1.2)	46.1 (0.9)	51.2 (0.8)
SES tertiles (%, SE)			
Low	35.2 (1.4)	32.0 (1.3)	33.3
Middle	32.0 (1.2)	32.8 (0.8)	33.3
High	32.8 (1.5)	35.2 (1.3)	33.3
Health Behaviors			
Weekly moderate or vigorous physical activity	76.7 (1.2)	70.0 (0.9)	72.8 (0.8)
Current smoker	15.8 (1.0)	12.8 (0.6)	14.1 (0.6)
Alcohol use >= 2d/week	37.7 (1.3)	22.1 (0.9)	28.6 (0.9)
Health Conditions			
Hypertension	44.9 (1.3)	46.3 (0.9)	45.7 (0.8)
Heart disease	19.9 (1.0)	14.2 (0.6)	16.6 (0.6)
Stroke	3.3 (0.4)	2.7 (0.2)	2.9 (0.2)
Lung disease	5.8 (0.4)	8.0 (0.5)	7.1 (1.2)
Cancer	11.0 (0.7)	11.3 (0.4)	11.2 (0.4)
Emotional/psychiatric problem	11.2 (0.8)	19.6 (0.7)	16.1 (0.5)
Pain	26.0 (0.9)	33.7 (0.9)	30.5 (1.5)
Urinary incontinence	2.2 (0.3)	11.7 (0.5)	7.7 (0.4)
BMI (mean, SE)	28.6 (0.1)	28.5 (0.1)	28.5 (0.1)
Obese (BMI>=30)	31.0 (1.0)	31.9 (1.0)	31.5 (0.7)

SES: Socio-economic status, BMI: Body mass index, SE: standard error. All percentages and standard errors weighted for complex sample design features.

Table 2.2. Prevalence of chronic sleep disturbances at baseline by gender and race/ethnicity*.

				Men				Women			
	Men	Women		White	Black	Hispanic		White	Black	Hispanic	
	% (SE)	% (SE)	p	% (SE)	% (SE)	% (SE)	p	% (SE)	% (SE)	% (SE)	p
Trouble Most of the Time	n=2778	n=4668		n=2310	n=264	n=204		n=3697	n=607	n=364	
Falling Asleep	6.9 (0.7)	15.1 (0.8)	**<0.001**	6.7 (0.7)	9.2 (2.6)	7.2 (2.0)	0.550	14.8 (0.9)	15.1 (1.3)	20.0 (2.8)	0.100
Waking up at night	21.8 (0.9)	28.0 (0.8)	**<0.001**	23.0 (1.0)	12.0 (2.0)	15.2 (3.2)	**0.001**	29.5 (0.9)	20.6 (1.7)	18.4 (2.6)	**0.001**
Waking up too early in morning	9.9 (0.7)	13.8 (0.6)	**<0.001**	9.9 (0.7)	11.9 (2.8)	8.6 (2.2)	0.602	13.3 (0.7)	14.5 (1.3)	18.7 (2.2)	**0.016**
1+ chronic sleep problems	28.2 (1.1)	37.1 (0.9)	**<0.001**	29.1 (1.2)	21.8 (3.0)	22.6 (4.4)	0.073	38.2 (1.1)	30.5 (1.9)	31.7 (3.3)	**0.009**

*All percentages are weighted and standard errors (SE) account for the complex sample design. Comparisons between and within gender with Rao-Scott Chi-square test statistic. Significant values in bold ($p<0.05$)

Table 2.3. 2006 baseline characteristics and diabetic status over prospective follow-up 2006-2014.

	Men		Women	
	Not diabetic	Incident diabetes	Not diabetic	Incident diabetes
	n=2,286	n=492	n=3,957	n=711
	% (SE)	% (SE)	% (SE)	% (SE)
2006 Demographic Characteristics				
Age (mean yrs, SE)	62.9 (5.3)	62.7 (6.8)	64.0 (5.5)	63.6 (6.7)
Race/Ethnicity				
White/other, non-Hisp	88.7 (1.0)	79.4 (2.5)	86.8 (1.0)	73.7 (2.1)
Black, non-Hisp	5.8 (0.6)	11.6 (1.6)	7.2 (0.6)	15.2 (1.6)
Hispanic	5.5 (0.7)	9.0 (1.7)	6.0 (0.9)	11.1 (1.8)
Education (mean yrs, SE)	14.0 (0.1)	13.2 (0.2)	13.4 (0.1)	13.0 (0.3)
HS degree or less	38.1 (1.4)	46.4 (2.7)	47.9 (1.1)	55.9 (2.2)
Some college or degree	61.9 (1.4)	53.6 (2.7)	52.1 (1.1)	44.1 (2.2)
Currently married	75.4 (1.4)	69.9 (2.3)	62.5 (1.0)	55.0 (2.2)
Currently working	59.1 (1.2)	55.8 (2.7)	45.9 (1.0)	46.8 (2.2)
SES Low	33.0 (1.5)	45.5 (3.1)	30.0 (1.4)	43.9 (2.2)
SES Middle	32.2 (1.3)	30.8 (2.8)	33.1 (0.9)	31.2 (1.8)
SES High	34.8 (1.6)	23.7 (2.4)	36.9 (1.4)	24.9 (2.0)
2006 Health Behaviors				
Weekly moderate or vigorous physical activity	77.3 (1.2)	73.9 (2.2)	70.9 (1.0)	64.8 (2.3)
Current smoker	15.5 (1.0)	16.9 (2.0)	12.7 (0.6)	13.5 (1.3)
Alcohol use >= 2days/week	39.3 (1.4)	29.6 (2.5)	23.7 (1.0)	12.4 (1.4)
2006 Health Conditions				
Hypertension	41.5 (1.5)	61.0 (2.4)	43.3 (0.9)	63.8 (2.1)
Heart disease	18.2 (0.9)	27.5 (2.5)	14.0 (0.5)	15.6 (1.6)
Stroke	3.1 (0.3)	4.4 (1.0)	2.4 (0.3)	3.9 (0.7)
Lung disease	5.6 (0.5)	7.0 (1.4)	7.5 (0.5)	11.0 (1.3)
Cancer	11.1 (0.7)	10.4 (1.5)	11.4 (0.5)	10.7 (1.1)
Emotional/psychiatric problem	11.3 (0.9)	10.9 (1.7)	18.9 (0.8)	23.4 (1.7)
Pain	25.1 (1.1)	30.1 (2.3)	32.6 (0.9)	40.4 (2.1)
Urinary incontinence	2.0 (0.4)	2.6 (0.8)	11.1 (0.6)	14.9 (1.3)
BMI (mean, SE)	28.0 (0.1)	31.4 (0.3)	28.0 (0.1)	31.1 (0.3)
Obese (BMI>=30)	26.6 (1.1)	52.0 (2.7)	28.7 (1.0)	51.0 (1.9)
2006 Sleep Disturbances				
Chronic trouble falling asleep	6.4 (0.7)	9.5 (1.7)	14.2 (0.8)	20.5 (1.7)
Chronic trouble waking up at night	21.3 (1.0)	24.2 (2.6)	27.2 (0.9)	32.3 (2.0)
Chronic trouble waking too early in morning	9.4 (0.7)	12.4 (2.0)	13.3 (0.7)	16.6 (2.1)
1+ chronic sleep disturbance	27.3 (1.3)	32.2 (2.8)	36.0 (1.1)	44.2 (1.8)

Baseline characteristics measured in 2006. Incident diabetes as reported between 2008-2014. SES: Socio-economic status, BMI: Body mass index, SE: standard error. All percentages and standard errors weighted for complex sample design features.

Table 2.4. Eight-year follow-up rates of diabetes by chronic sleep disturbance, gender and race/ethnicity.

Men		>= 1 Chronic Sleep Disturbance		Women		>= 1 Chronic Sleep Disturbance	
All		**Yes**	**No**	**All**		**Yes**	**No**
n=2,778	Number of individuals	800	1978	n=4,668	Number of individuals	1700	2968
	# incident diabetes	152	340		# incident diabetes	295	416
	Person Years (PY)	6400	15824		Person Years (PY)	13600	23744
	Crude incidence per 10,000 PY	**237.5**	**214.9**		Crude incidence per 10,000 PY	**216.9**	**175.2**
Black				**Black**			
n=264	Number of individuals	57	207	n=607	Number of individuals	178	429
	# incident diabetes	18	57		# incident diabetes	57	100
	Person Years (PY)	456	1656		Person Years (PY)	1424	3432
	Crude incidence per 10,000 PY	**394.7**	**344.2**		Crude incidence per 10,000 PY	**400.3**	**291.4**
Hispanic				**Hispanic**			
n=204	Number of individuals	41	163	n=364	Number of individuals	115	249
	# incident diabetes	11	44		# incident diabetes	30	56
	Person Years (PY)	328	1304		Person Years (PY)	920	1992
	Crude incidence per 10,000 PY	**335.4**	**337.4**		Crude incidence per 10,000 PY	**326.1**	**281.1**
White				**White**			
n=2,310	N	702	1608	n=3,697	Number of individuals	1407	2290
	# incident diabetes	123	239		# incident diabetes	208	260
	Person Years (PY)	5616	12864		Person Years (PY)	11256	18320
	Crude incidence per 10,000 PY	**219.0**	**185.8**		Crude incidence per 10,000 PY	**184.8**	**141.9**

Crude incidence rates of diabetes after 8 years of follow-up. Incident diabetes based on self-report or hemoglobin A1C >=6.5 mg/dl.

Table 2.5. Cox proportional model estimates of hazard ratios of developing diabetes within 8 years of follow-up among women.

	Unadjusted	Adjusted-1	Adjusted-2	Adjusted-3	Adjusted-4	Adjusted-5	Adjusted-Time Varying
1/+ Sleep Problems	**1.37 (1.17-1.60)**	**1.43 (1.23-1.67)**	**1.40 (1.19-1.63)**	**1.31 (1.12-1.53)**	**1.30 (1.11-1.51)**	**1.29 (1.11-1.49)**	**1.27 (1.08-1.50)**
Age		**1.24 (1.05-1.45)**	**1.27 (1.08-1.50)**	**1.21 (1.04-1.42)**	**1.21 (1.04-1.41)**	**1.22 (1.05-1.43)**	**1.23 (1.06-1.43)**
Black		**2.35 (1.88-2.93)**	**1.96 (1.56-2.44)**	**1.59 (1.28-1.98)**	**1.57 (1.26-1.95)**	**1.59 (1.28-1.98)**	**1.56 (1.25-1.95)**
Hispanic		**2.07 (1.62-2.65)**	**1.80 (1.39-2.33)**	**1.81 (1.37-2.38)**	**1.75 (1.33-2.31)**	**1.80 (1.37-2.37)**	**1.77 (1.33-2.35)**
Low SES			**1.69 (1.36-2.10)**	**1.40 (1.12-1.76)**	**1.28 (1.02-1.61)**	1.20 (0.95-1.53)	1.18 (0.92-1.50)
Middle SES			**1.30 (1.05-1.62)**	1.19 (0.95-1.49)	1.14 (0.91-1.42)	1.10 (0.88-1.37)	1.08 (0.86-1.34)
Obese				**1.89 (1.59-2.26)**	**1.84 (1.54-2.19)**	**1.83 (1.55-2.17)**	**1.68(1.32-2.13)**
Hypertension				**1.76 (1.47-2.11)**	**1.76 (1.47-2.11)**	**1.78 (1.47-2.14)**	**1.35(1.09-1.67)**
Physical activity					0.98 (0.80-1.18)	0.97 (0.80-1.18)	0.98 (0.79-1.20)
Alcohol use					**0.62 (0.48-0.81)**	**0.61 (0.47-0.80)**	0.75 (0.55-1.02)
Current smoker					1.12 (0.88-1.43)	1.11 (0.87-1.41)	1.07 (0.77-1.51)
Pain						1.01 (0.85-1.21)	1.04 (0.87-1.24)
Emotional problems						1.15 (0.93-1.42)	1.16 (0.81-1.65)
Incontinence						1.09 (0.86-1.38)	1.08 (0.81-1.43)
Heart disease						0.93 (0.72-1.20)	0.83 (0.63-1.10)
Currently married						0.90 (0.73-1.10)	0.76 (0.56-1.03)
Currently working						1.21 (0.99-1.48)	1.15 (0.94-1.40)

SES: socio-economic status; Reference groups: white, high socio-economic status. Values in bold are statistically significant. Adjusted models 1-5 are adjusted for the variables shown. Adjusted time-varying is adjusted for baseline values and time-varying values of obesity, hypertension, physical activity, alcohol use, smoking status, pain, emotional problems, incontinence, heart disease, marital status and employment status.

Table 2.6. Cox proportional model estimates of hazard ratios of developing diabetes within 8 years of follow-up among men.

	Unadjusted	Adjusted-1	Adjusted-2	Adjusted-3	Adjusted-4	Adjusted-5	Adjusted-Time Varying
1/+ Sleep Problems	1.25 (0.96-1.62)	1.29 (0.99-1.69)	1.27 (0.98-1.66)	1.23 (0.95-1.58)	1.22 (0.94-1.58)	1.22 (0.94-1.57)	1.14 (0.88-1.48)
Age		**1.24 (1.01-1.51)**	**1.28 (1.04-1.58)**	1.20 (0.98-1.48)	1.21 (0.98-1.49)	1.22 (0.99-1.51)	1.21 (0.97-1.52)
Black		**2.11 (1.49-2.98)**	**1.79 (1.27-2.52)**	**1.63 (1.16-2.29)**	**1.57 (1.11-2.22)**	**1.59 (1.12-2.26)**	**1.62 (1.15-2.29)**
Hispanic		**1.69 (1.20-2.39)**	**1.48 (1.06-2.07)**	**1.44 (1.01-2.05)**	1.41 (1.00-1.99)	**1.48 (1.05-2.09)**	**1.55 (1.10-2.19)**
Low SES			**1.76 (1.33-2.32)**	**1.60 (1.23-2.08)**	**1.50 (1.15-1.96)**	**1.38 (1.05-1.83)**	**1.40 (1.05-1.85)**
Middle SES			**1.36 (1.02-1.81)**	1.24 (0.93-1.65)	1.20 (0.90-1.60)	1.16 (0.88-1.54)	1.15 (0.89-1.50)
Obese				**2.30 (1.82-2.91)**	**2.29 (1.82-2.90)**	**2.37 (1.87-3.02)**	**1.98 (1.52-2.59)**
Hypertension				**1.65 (1.30-2.09)**	**1.67 (1.31-2.13)**	**1.58 (1.25-2.00)**	1.19 (0.93-1.52)
Physical activity					1.00 (0.82-1.22)	1.00 (0.83-1.22)	0.99 (0.82-1.20)
Alcohol use					**0.77 (0.61-0.98)**	**0.77 (0.61-0.98)**	0.81 (0.60-1.08)
Current smoker					1.16 (0.88-1.52)	1.13 (0.87-1.47)	1.27 (0.90-1.78)
Pain						1.04 (0.83-1.30)	1.10 (0.85-1.43)
Emotional problems						0.79 (0.53-1.16)	**0.62 (0.40-0.97)**
Incontinence						1.08 (0.56-2.10)	1.28 (0.65-2.49)
Heart disease						**1.48 (1.19-1.83)**	1.24 (0.95-1.64)
Currently married						**0.76 (0.59-0.97)**	0.69 (0.47-1.00)
Currently working						1.01 (0.77-1.33)	0.96 (0.72-1.30)

SES: socio-economic status; Reference groups: white, high socio-economic status. Values in bold are statistically significant. Adjusted models 1-5 are adjusted for the variables shown. Adjusted time-varying is adjusted for baseline values and time-varying values of obesity, hypertension, physical activity, alcohol use, smoking status, pain, emotional problems, incontinence, heart disease, marital status and employment status.

Chapter 3 Type II Diabetes and the Development of Chronic Sleep Disturbances in Older Adults.

Abstract

Study Objective: Chronic sleep disturbances can lead to lack of glycemic control among diabetic and non-diabetic individuals. While previous studies have shown chronic sleep disturbances to be a risk factor in the development of diabetes, it is not known whether incident diabetes is associated with developing chronic sleep disturbances. This study assesses the odds of developing a chronic sleep disturbance within four years among adults with a recent diagnosis of diabetes compared to those with prevalent diabetes and those without a diagnosis of diabetes.

Methods: Participants were selected from the Health and Retirement Study (n=8,015). Participants who completed an interview in 2010 and were free of chronic sleep disturbances were categorized as not diabetic, having a recent diagnosis of type II diabetes or as previously diagnosed with type II diabetes. Chronic sleep disturbances were assessed after four years and defined as self-reported trouble falling asleep, waking up at night or waking up too early most of the time. Logistic regression models were estimated to determine the odds of developing a chronic sleep disturbance after adjusting for demographic, lifestyle and health conditions.

Results: At baseline, 5.3% of men and 2.9% of women reported a diagnosis of diabetes since 2009. After four years, 29.1% of women and 19.3% of men reported onset of one or more chronic sleep disturbances. Although not significant, men and women without diabetes reported lower rates of sleep disturbances (16.7% and 18.6% respectively). Women with incident diabetes

had an 80% greater odds of developing a chronic sleep disturbance within four years than those without diabetes (OR 1.80; 95% CI 1.01-3.20). However, the odds were attenuated and no longer significant after adjusting for demographic, lifestyle and health conditions (OR 1.63; 95% CI 0.86-3.12). While the direction of the association was similar in men, unadjusted and adjusted logistic models were not statistically significant (fully adjusted model OR 1.14; 95% CI 0.69-1.90).

Conclusions: This study supports previous cross-sectional findings that a recent diagnosis of diabetes may increase the odds of developing a chronic sleep disturbance, especially in women. Given the negative effect of chronic sleep disturbances on glycemic control, the presence of sleep disturbances should be monitored among newly diagnosed diabetics. Early detection and intervention can reduce the additional burden and risk for deleterious outcomes in this growing population.

Key words cohort, sleep disturbance, sleep quality, diabetes, incident

Introduction

Diabetes is the most frequently diagnosed chronic condition and the chronic disease that is increasing at the most rapid rate in the world (1-4). Between 1980 and 2008, the U.S. population aged 65 and older experienced the greatest increase in the prevalence of diabetes with an increase from 8% to nearly 20% (5). Ensuring glycemic control among this population is critical to reduce the individual and societal burden related to poor glycemic control which includes increased treatments costs, lost days of work and reductions in quality of life. The costs associated with diagnosed diabetes are staggering at both the societal and individual level. In 2008, it was estimated that one out of every five dollars spent on health care in the United States was spent on diabetic patients (6). The total estimated cost of diagnosed diabetes was $174 billion in 2007. In 2012, it was estimated that the total annual cost of diagnosed diabetes had increased to $245 billion, a 41% increase in five years. Seventy-two percent (72%) of the $245 billion was attributable to direct medical costs and the remainder due to lost productivity. At the individual level, the total annual health care costs of those with diagnosed diabetes are close to $14,000, likely due to the increased risk of comorbid conditions in this population. Close to $8,000, or 58% of the annual medical costs incurred, were attributable to the diagnosed diabetes including doctor's visits, medical tests and medication. These increased health care costs are likely to come at a time in life in which health care coverage is extremely expensive and prescription coverage is limited for a large portion of the affected population. Over two-thirds of these costs are covered by the government (Medicare, Medicaid, the military) and by uninsured individuals. With the cost of insulin increasing three-fold in the last ten years, the undue burden on our aging population must be addressed (7).

Both short term and chronic sleep disturbances, including sleep deprivation as well as sleep interruptions, impair glycemic control and reduce insulin sensitivity (8). While this is a concern for the population in general, reduced glycemic control is especially problematic among individuals with diabetes. Previous studies have shown disruptions in sleep duration as well as chronic sleep disturbances to be risk factors in the development of type II diabetes (9-18). Numerous cross-sectional studies have found that those with diabetes report sleep disturbances to a greater degree than those without diabetes (19-22). However, few studies have assessed whether incident diabetes is itself associated with the development of chronic sleep disturbances. There are several plausible mechanisms which may lead to the development of chronic sleep disturbances among individuals recently diagnosed with diabetes. This includes hyperglycemia experienced at night by those with diabetes which can lead to nocturia, a common reason for night wakening. Additionally, a period of adaptation to the new diagnosis, as well as new medications and required lifestyle changes, could lead to increased anxiety or depression both of which are associated with chronic sleep disturbances. Finally, it is likely that there is a bi-directional relationship in the association between inflammation and inflammatory processes, such as increased C-reactive protein and interleukin 6, and sleep disturbances (8, 23). Given that individuals with diabetes and chronic sleep disturbances have an increased risk for poor health outcomes, determining whether newly diagnosed type II diabetes is associated with the development of chronic sleep conditions is important. Reduced glycemic control as a result of chronic sleep disturbances could potentially lead to decreased quality of life and accelerate other negative outcomes associated with diabetes.

Several studies have demonstrated a U-shaped relationship between sleep duration and glycemic control (19). Among non-diabetic participants of NHANES, fasting and 2-hr insulin

and HbA1c levels results were significantly associated with short sleep, but attenuated after adjusting for BMI (21). Knutson and colleagues conducted a small study of African American volunteers and demonstrated that both sleep duration and quality were associated with HbA1c level (24). If individuals with a recent diagnosis of diabetes are at an increased risk of developing chronic sleep disturbances, a known risk factor for poor glycemic control, this offers an area of intervention and treatment that might plausibly reduce the individual and societal burden.

While previous studies have demonstrated the association between sleep duration and sleep quality on the development of diabetes, few have determined whether incident diabetes increases the odds of developing a sleeping disturbance. Those that do exist had small sample sizes and were not able to detect differences by gender (24-26). In our study, we assess the odds of developing a chronic sleep disturbance within four years among adults with a recent diagnosis of diabetes compared to adults with prevalent diabetes and those without a diagnosis of diabetes. We will also assess differences by gender given the higher rates of sleep disturbances typically reported in women, the inconclusive results of previous studies assessing the role of gender in the relationship between type II diabetes and sleep disturbances, as well as differences in inflammatory markers by gender (8, 10, 14, 27).

Methods

Participants

Health and Retirement Study

Participants were drawn from the Health and Retirement Study. The Health and Retirement Study is a national, longitudinal study representative of the U.S. population age 50 and older. The study began in 1992 and includes a new cohort of individuals age 50-55 every six years in order to maintain representation of the U.S. population in this age group as well as the older age groups as the study sample ages (28). Panel participants are interviewed every two years by

phone or in person. The complex sample design, including oversamples of Black and Hispanic participants, allows for broad population-based inferences (29). The Health and Retirement Study is approved by the University of Michigan Institutional Review Board and is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan.

Study Sample

Participants for the current study were selected from those who completed an HRS interview in 2010. Figure 3.1 provides a description of the sample. A total of 19,331 participants completed an interview in 2010. Participants who were interviewed by proxy or in a nursing home in 2006 were not eligible for inclusion in the study. Participants who missed an interview in 2010 or 2014, or were deceased after 2010 were not eligible for inclusion in the study. Participants with missing data on key covariates were excluded from the current analysis. Each wave of data collection, a random half of participants are selected for in-home anthropometric measurements including height and weight. Those who did not have height and weight measurements (n=6,784) in 2010 were excluded from the current study given the importance of obesity in assessing the relationship between diabetes and sleep disturbances. After exclusion for missing data on key covariates (n=196) and those who reported a chronic sleep disturbance at baseline (n=4,336), 8,015 participants remained in the sample.

Measures

Self-reported measures of demographic characteristics and health status were collected in 2010 and in 2014.

Exposure: Diabetes status

Diabetes status was categorized as not diabetic, a new case of diabetes or as having diabetes for two or more years based on self-report at the time of the interview in 2010 or the results of a hemoglobin A1C assay from a dried blood spot sample collected at the time of the interview. Participants were considered to be ***not diabetic*** if they reported that they had not received a medical diagnosis of diabetes and did not have an A1c result of 6.5mg/dL or greater. Participants were considered ***recently diagnosed with diabetes*** if they first reported a diagnosis of diabetes during their 2010 interview and stated that the diagnosis had occurred since 2009 or stated that they had not received a diagnosis or diabetes but had an A1c result of 6.5 mg/dl or greater. Participants were considered ***to have diabetes for two or more years*** if they had previously reported a diagnosis of diabetes and confirmed the diagnosis in their current interview.

Outcome: Sleep disturbances

Participants were asked three questions related to sleep disturbance in 2010 and 2014. The questions were:

How often do you have trouble falling asleep?

How often do you have trouble with waking up during the night?

How often do you have trouble with waking up too early and not being able to fall asleep again?

Three response options were offered for each of the questions: "Would you say most of the time, sometimes, or rarely or never?".

Several measures of chronic sleep disturbance were created based on the literature. Participants were categorized as having ***trouble falling asleep***, an indication of insomnia, if they responded "most of the time" to the question. Participants were categorized as having ***trouble staying asleep*** if they responded "most of the time" to either of the two questions on waking up

during the night or waking up too early. Participants were considered to have a ***chronic sleep disturbance*** if they responded "most of the time" to one or more of the three questions related to trouble sleeping.

Covariates: Demographic, health behaviors, health conditions

Demographic variables include self-reported age at the time of interview, gender, years of education and race/ethnicity. Respondents were categorized as Hispanic, non-Hispanic Black, non-Hispanic white/other based on responses to two separate questions on Hispanic ethnicity and race. Education level was categorized as less than high school, high school graduate, some college or college graduate. Educational level is considered a proxy measure of socio-economic status given the age and working status in the study population. Marital status was coded as currently married versus not married (including never married, separated/divorced and widowed). Work status was coded as currently working or not working.

Health behaviors of interest included self-reported measures of physical activity, current smoking status and current alcohol consumption. Participants who reported engaging in moderate or vigorous physical activity at least once a week on average were considered to be physically active. Respondents who reported that they were current cigarette smokers were categorized as smokers. Current alcohol consumption on two or more days per week was considered positive for alcohol consumption.

Other health conditions that were considered potential confounders or moderators in the association between diabetic status and chronic sleep disturbances were included based on self-report (Has a doctor or other medical professional ever told you that you have…"). Health conditions of interest included hypertension, heart disease, heart attack, stroke, lung diseases, cancer, emotional, nervous or psychiatric problems, depression, chronic pain, arthritis or urinary

incontinence. Body mass index (BMI) was calculated based on self-reported height and weight or height and weight measured by an interviewer during the in-home visit. A BMI of 25-29.9 was considered overweight and a BMI of 30 or greater was considered obese.

Statistical Analysis

Cases meeting inclusion criteria at baseline (2010) were merged with interview data collected in 2014. Descriptive data analysis of all baseline characteristics was conducted for all of the sample as well as with the exposure variables and the outcome variables. Mean values of continuous variables were compared using t-tests. Rao-Scott chi-square tests were utilized to assess the bivariate associations of categorical variables. All reported values were weighted for the complex survey design and survey non-response. Complex survey procedures were used in data analysis to compute 95% confidence intervals to account for the multi-stage cluster sample design.

Logistic regression models were estimated to determine the odds, among those who did not report a chronic sleep disturbance at baseline, of developing a chronic sleep disturbance after four years among participants without diabetes, participants with a recent diagnosis of diabetes and participants with a prior diagnosis of diabetes. Multiple logistic regression models were estimated to assess the odds of developing a chronic sleep disturbance given the participant's baseline diabetic status. Regression models were stratified by gender. Three logistic regression models were calculated per gender to determine the impact of demographic, behavioral and health risk factors on the development of chronic sleep conditions. Model 1 assessed the unadjusted odds ratio of developing chronic sleep disturbance by diabetic status. Model 2 adjusted for demographic characteristics including age, race/ethnicity and education. Model 3 adjusted for the model 2 variables as well as other lifestyle and health covariates including

current employment and marital status, physical activity, alcohol consumption, smoking status, obesity, hypertension, heart disease, chronic pain, depression, incontinence and arthritis. Comparisons were made between those recently diagnosed with diabetes versus those with a prior diagnosis of diabetes, compared to those without a diagnosis of diabetes (reference group). First order interactions were assessed among key predictors. Odds ratios and 95% confidence intervals were calculated for all covariates in each model. The complex sample design characteristics (strata, cluster and respondent weights) were utilized at all stages of analysis. All statistical tests were two-sided at a significance level of .05. SAS v9.4 (SAS Institute, Inc., Cary, NC) was used for data analysis.

Results

Weighted estimates of demographic characteristics, health behaviors and health conditions of the study population at baseline are shown in Table 3.1. Just over half of the study population was female (53.5%) and the average age of the population represented by the eligible sample was 61.9 years (range 50-101). Differences were observed between men and women in most demographic characteristics. Men in the study population were more likely to be younger, non-Hispanic White/Other, have a college degree, and to be currently working as well as married ($p<0.001$ for all observed differences). Additionally men were more likely to report engaging in moderate or vigorous physical activity on a weekly basis and consuming alcohol on two or more days per week than women. Women were less likely to have newly diagnosed diabetes but more likely to report having a previous diagnosis of diabetes prior to 2009. Half the population of men and women had hypertension. With the exception of stroke, women reported higher rates of each chronic condition than men including arthritis, lung disease, cancer, depression, pain and urinary incontinence. The greatest differences were for arthritis (women 51.6%, men 35.6%), depression

(women 21.7%, men 11.5%), pain (women 30.1%, men 24.0%) and urinary incontinence (women 24.8%, men 7.1%). While the mean BMI was similar for men and women, 29.4 and 29.0 respectively, women had slightly higher rates of obesity whereas men were more likely to be overweight. Differences between gender were statistically significant at $p<0.001$.

Women were more likely than men to report chronic sleep disturbances after four years for each type of sleep disturbance. Men reported difficulty staying asleep as the most frequent sleep disturbance. Among men, those with existing diabetes reported difficulty staying asleep slightly more often than those who were newly diagnosed with diabetes. However, men with newly diagnosed diabetes were more likely than those without diabetes and those with existing diabetes to report one or more chronic sleep disturbance after four years (19.3 vs 16.7 vs 17.1, respectively). These differences were not statistically significant for men. Close to one-third of women with newly diagnosed diabetes reported the development of a chronic sleep disturbance after four years. In women, the prevalence of chronic sleep disturbances were 37% higher in those with newly diagnosed diabetes than those with existing diabetes, and 56% greater than those without diabetes. Women with newly diagnosed diabetes were more than twice as likely as those without diabetes to report chronic difficulty falling asleep (18.4% vs 8.1%). However, these differences were not statistically significant within women.

The odds of developing a chronic sleep disturbance within four years are shown in Table 3.3. Men with recently diagnosed diabetes were 19% more likely to develop a chronic sleep disturbance within four years than those without diabetes (OR 1.19; 95% CI 0.71-1.99). However, this result was not significant and was slightly attenuated after adjustment for demographic and lifestyle covariates as well as health conditions which included obesity, hypertension, chronic pain, arthritis, ever had depression and incontinence (OR 1.14; 95% CI

0.69-1.90). In the fully adjusted model for men, those who reported that they were currently working at the time of the baseline interview were 25% less likely to develop a chronic sleep disturbance within four years (OR 0.75; 95% CI 0.60-0.95). However, in the fully adjusted model, men who reported experiencing chronic pain or ever experiencing a depressive episode were more likely to develop a chronic sleep disturbance within four years than those without pain or depression (pain OR 1.39, 95%CI 1.04-1.85; depression OR 1.56, 95%CI 1.08-2.26). These results are shown in supplemental table 4.1 In the unadjusted model, women with recently diagnosed diabetes were 80% more likely to develop a chronic sleep disturbance within four years than those without diabetes (OR 1.80; 95% CI 1.01-3.20). Although the direction of the association was maintained, the association was attenuated after adjustment for demographic and lifestyle covariates as well as chronic health conditions (OR 1.63; 95%CI 0.86-3.09).

In the fully adjusted model for women, being 70 years of age or older, Black, and currently working were all protective against the development of a chronic sleep disturbance after four years. Those between the ages of 70 to 79 were 30% less likely to develop a chronic sleep disturbance and those who were 80 years or older at baseline were 41% less likely than women between the ages of 50 to 59 to develop a chronic sleep disturbance. Non-Hispanic Black women were 23% less likely to develop a chronic sleep disturbance after four years than non-Hispanic white women (OR 0.77; 95%CI 0.60-0.98). Women who reported that they were currently working during their baseline interview were 31% less likely to develop a chronic sleep disturbance than those who were not working at that time (OR 0.68; 95% CI 0.53-0.87). However, women with other chronic conditions, including pain, depression, incontinence and arthritis, were significantly more likely to report chronic sleep disturbances after four years (supplemental table 4.1). First-order interactions between diabetes status and pain, depression,

incontinence and arthritis were assessed in the fully adjusted models for men and women. The interaction terms were not statistically significant.

Discussion

In this population-based study of community-dwelling older men and women, we find that women report higher rates of chronic sleep disturbances than men and that those with a recent diagnosis of diabetes report higher rates of chronic sleep disturbances after four years than those without diabetes. Close to thirty-percent of women with newly diagnosed type II diabetes and twenty-percent of men reported the development of a chronic sleep disturbance within four years of receiving a diagnosis of diabetes. Among the initial study population, 47.5% of women and 33.5% of men with a recent diagnosis of diabetes reported having one or more chronic sleep disturbances at baseline. While these individuals were excluded from the current study, this indicates that over 75% of women and over 50% of men will have experienced a chronic sleep disturbance at the time of diagnosis or within four years of receiving a diagnosis of diabetes. Given the effects of chronic sleep disturbances on glycemic control, this is a grave concern.

Women with recently diagnosed diabetes had an 80% greater (unadjusted) odds of developing a chronic sleep disturbance within four years than those without diabetes. The odds decreased to 18% for those with longer-term type II diabetes indicating that the development of a new chronic sleep disorder may be most likely to occur within a few years of diagnosis. While the association was attenuated in women after controlling for demographic characteristics, behavioral factors and health conditions, the magnitude of the association continued to indicate the increased odds of developing a chronic sleep condition in women with a recent diagnosis of diabetes. Women aged 70 and older at the time of diagnosis as well as non-Hispanic Black women appear to have a decreased risk of developing a chronic sleep disturbance. However, the

contribution of other chronic conditions to the development of a chronic sleep disturbance cannot be overlooked. While the associations in men are not significant, the role of pain and depression in the development of chronic sleep disturbances is observed as well. The results in both women and men provide support for the potential pathways of the psychosocial impact of a new diagnosis, nocturia and inflammation in the development of chronic sleep disturbances among those recently diagnosed with diabetes.

While previous studies have found that chronic sleep disturbances appear to precede or coincide with the diagnosis of diabetes, the results of this study show that the development of chronic sleep disturbances continues to be of clinical importance among older adults with a new diagnosis of diabetes, and potentially to a greater degree among women than men. The potential mechanisms leading to the differences in this association between men and women must be considered, including differences in hormonal, psychosocial and environmental conditions as well as the impact of the comorbidity of chronic sleep disturbances and diabetes with other existing conditions such as chronic pain, depression and anxiety and arthritis. Previous studies have primarily focused on sleep duration, rather than sleep quality. To our knowledge, this is the first study to examine the association between sleep quality and incident diabetes, rather than prevalent diabetes.

This study has numerous strengths including the large, nationally representative sample and the longitudinal study design. Additionally, this study provides information on sleep quality and adds to the growing body of literature on the importance of sleep quality in addition to the impact of sleep duration. The greatest limitation of the current study is that both the exposure and outcome are based on self-report. The use of hemoglobin A1c results to categorize diabetics increased the diagnosis of incident diabetics by 33%. However, hemoglobin A1c was only

measured in a random half of the population. Thus, we might estimate that approximately 80 additional individuals with undiagnosed diabetes exist in our study population. Additionally, measures of sleep quality were collected at baseline and after four years. While a goal of the current study was to assess the development of chronic sleep disturbances, rather than transient disturbances occurring shortly after the diagnosis, it is possible that our results under estimate the magnitude of sleep disturbances given the time lapse in assessment. The incorporation of clinically validated measures of sleep disturbance, such as actigraphy, may help increase the sensitivity of the measurement of sleep disturbances as compared to self-reported measures of sleep quality. Additionally, we cannot rule out the role of sleep apnea in the current association or other unmeasured confounders.

Current assessment and treatment guidelines for individuals recently diagnosed with diabetes do not include the assessment of sleep disturbances. Given the negative repercussions of untreated chronic sleep disturbances on glycemic control, chronic sleep conditions should be assessed at follow-up visits as well as initial visits. Such discussions are especially important among individuals with multiple chronic conditions as they appear to be at increased risk of developing chronic sleep disturbances. Incorporating discussions on sleep hygiene, as well as detecting the need for pharmacological treatment of chronic sleep disturbances, should be a standard of care among those treating individuals with type II diabetes.

References

1. International Diabetes Federation (IDF) Diabetes Atlas. (2010). Prevalence estimates of diabetes mellitus (DM), 2010. Brussels, Belgium.

2. Scott SK, Harris RE. Epidemiology of diabetes mellitus. In Epidemiology of Chronic Disease: Global Perspectives. Jones & Bartlett Learning, LLC, 2013. p.3 75-416.

3. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053.

4. Narayan KMV, Boyle J, Thompson T, et al. Lifetime risk for diabetes mellitus in the United States. JAMA 2003; 290(14):1884-1890. doi 10.1001/jama290.14.1884.

5. Geiss L, Wang J, Cheng Y, Thompson T, Barker L, Li Y, Albright A, Gregg E. Prevalence and Incidence Trends for Diagnosed Diabetes Among Adults Aged 20 to 79 Years, United States, 1980-2012. JAMA. 2014;312(12):1218-1226.

6. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013;36(4):1033-46.

7. The Staggering Costs of Diabetes; 2015. Available from diabetes.org/advocacy/news-events/cost-of-diabetes.html. Accessed 9 Nov 2017.

8. Broussard J, Knutson KL. Sleep and metabolic disease. In Sleep, Health, and Society: From Aetiology to Public Health. Cappuccio F, Miller M, Lockley S. New York, Oxford University Press. 2010, p. 111-140.

9. Kawakami N, Takatsuka N, Shimizu H. Sleep disturbance and onset of type 2 diabetes. Diabetes Care 2004;27:282-283.

10. Meisinger C, Heier M, Loewel H. MONICA/KORA Augsburg Cohort Study. Sleep disturbance as a predictor of type 2 diabetes mellitus in men and women from the general population. Diabetologia 2005;48:235-241.

11. Beihl D, Liese A, Haffner S. Sleep Duration as a Risk Factor for Incident Type 2 Diabetes in a Multiethnic Cohort. Annals of Epidemiology. 2009;19.5:351-357.

12. Zizi F, Pandey A, Murrray-Bachmann R, Vincent M, McFarlane S, Ogedegbe G, Girardin JL, Race/ethnicity, sleep duration, and diabetes mellitus: analysis of the National Health Interview Survey. The American Journal of Medicine. 2012;125: 2. 162-167.

13. Ayas N, White D, Al-Delaimy W, Manson J, Stampfer M, Speizer F, Patel S, Hu F. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care. 2003. 26:2,380-384.

14. Gangwish J, Heymsfield S, Boden-Albala B, Bujis R, Kreier F, Pickering T, Rundle A, Zammit G, Malaspina D. Sleep duration as a risk factor for diabetes incidence in a large US sample. Sleep.

2007. 20:12,1667-1673.

15. Schan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, Rong Y, Jackson C, Hu F, Liu L. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care. 2015. 38(3):529-37.

16. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33:414-420.

17. Shan Z, Ma H, Xie M, Yan P, Guo Y, Bao W, et al. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care. 2015. 38(3):529-537.

18. Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. Diabetes Care 2005;28:2762-2767.

19. Kim BK, Kim BS, An SY, Lee MS, Choi YJ, Han SJ, Chung YS, Lee KW, Kim DJ. Sleep duration and glycemic control in patients with diabetes mellitus: Korea National Health and Nutrition Examination Survey 2007-2010. J Korean Med Sci. 2013 Sep;28(9):1334-9.

20. Ohkuma T, Fujii H, Iwase M, Kikuchi Y, Ogata S, Idewaki Y, Ide H, Doi Y, Hirakawa Y, Nakamura U, Kitazono T. Impact of sleep duration on obesity and the glycemic level in patients with type 2 diabetes: the Fukuoka Diabetes Registry. Diabetes Care. 2013 Mar;36(3):611-7.

21. Ford E, Wheaton A, Chapman D, Li C, Perry G, Croft J. Associations between self-reported sleep duration and sleeping disorder with concentrations of fasting and 2-h glucose, insulin, and glycosylated hemoglobin among adults without diagnosed diabetes. J Diabetes. 2014;6(4):338-350.

22. Knutson KL, Wu D, Patel S, Loredo J, Redline S, Cai J, Gallo L, Mossavar-Rahmani Y, Ramos A, Teng Y, Daviglus M, Zee P. Association between sleep timing, obesity, diabetes: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Cohort Study. Sleep. 2017. 40.4:1-8.

23. Ferrie JE, Kumari M, Salo P, Singh-Manoux A, Kivimaki M. Sleep epidemiology- a rapidly growing field. International Journal of Epidemiology. 2011.(40):1431-1437.

24. Knutson K, Ryden A, Mander B, VanCauter E. Role of Sleep Duration and Quality in the Risk and Severity of Type 2 Diabetes Mellitus. Arch Intern Med. 2006;166:1768-1774.

25. Cuellar NG, Ratcliffe SJ. A comparison of glycemic control, sleep, fatigue, and depression in type 2 diabetes with and without restless legs syndrome. Journal of Clinical Sleep Medicine. 2008. 4:50-56.

26. Trento M, Broglio F, Riganti F et al. Sleep abnormalities in type 2 diabetes may be associated with glycemic control. Acta Diabetologia. 2008. 45:225-229.

27. Bjorkelund C, Bondyr-Carlsson D, Lapidus L. Sleep disturbances in midlife unrelated to 32-year diabetes incidence: the prospective population study of women in Gothenburg. Diabetes Care. 2005. 28:2739-2744.

28. Sonnega A, Faul JD, Ofstedal MB et al. Cohort profile: The Health and Retirement Study (HRS). International Journal of Epidemiology. 2014. 43:576-585.

29. Heeringa SG, Connor J. Technical Description of the Health and Retirement Study Sample Design. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 1995.

30. Crimmins EM, Guyer H, Langa KM, Ofstedal MB, Wallace RB, Weir DR. Documentation of Physical Measures, Anthropometrics and Blood Pressure in the Health and Retirement Study. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 2008.

Figure 3.1 Study population

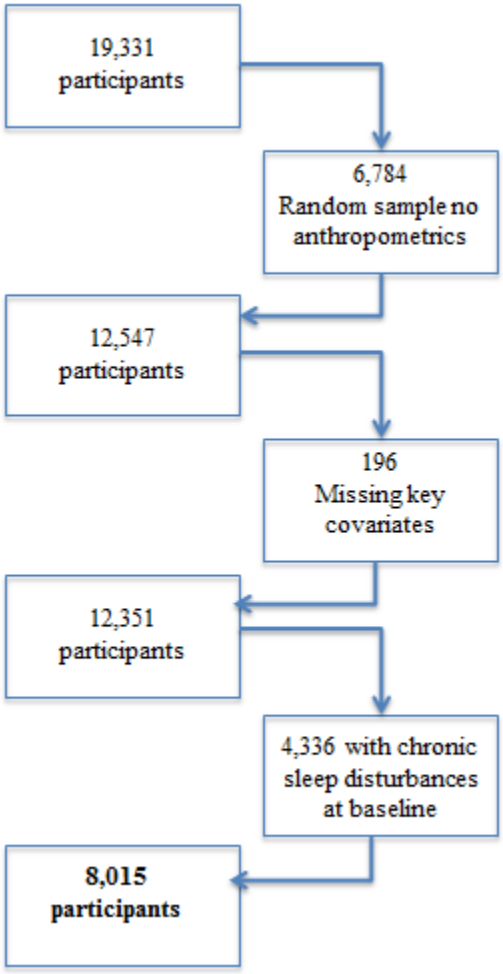


Table 3.1 Baseline characteristics of the study population by gender.

	Men n=3075	Women n= 4288	All n= 8015
Demographic Characteristics	**% (SE)**	**% (SE)**	**% (SE)**
Age (mean yrs, SE)	61.1 (0.3)	62.7 (0.3)	61.9 (0.3)
Age categories*			
50-59 years	55.4 (1.6)	48.4 (1.6)	51.9 (1.5)
60-69 years	26.3 (1.1)	28.0 (1.1)	27.1 (0.9)
70-79 years	12.3 (0.8)	14.1 (0.7)	13.2 (0.7)
80 or older	6.0 (0.5)	9.5 (0.6)	7.8 (0.5)
Race/Ethnicity*			
White/other, non-Hispanic	80.2 (1.6)	78.0 (1.6)	79.1 (1.5)
Black, non-Hispanic	10.6 (0.8)	13.1 (1.1)	11.8 (0.9)
Hispanic	9.2 (1.4)	8.9 (1.4)	9.1 (1.4)
Education*			
< High School	14.1 (0.9)	12.9 (1.0)	13.5 (0.9)
High School	26.4 (1.0)	31.6 (1.1)	29.0 (0.8)
Some College	25.6 (1.1)	26.8 (1.0)	26.2 (0.9)
College degree	33.9 (1.4)	28.7 (1.2)	31.3 (1.0)
Currently married*	70.6 (1.2)	56.6 (1.0)	63.6 (0.9)
Currently working*	57.3 (1.3)	49.2 (1.3)	53.2 (1.2)
Health Behaviors			
Weekly moderate or vigorous phys activity*	74.3 (0.9)	67.2 (1.1)	70.7 (1.9)
Current smoker**	17.6 (0.8)	14.4 (0.7)	16.0 (0.6)
Alcohol use >= 2d/wk*	36.5 (1.2)	22.8 (1.0)	29.6 (3.1)
Health Conditions			
Diabetes status*			
Recently diagnosed (2009 or later)	5.3 (0.6)	2.9 (0.4)	4.1 (0.4)
Diabetes since 2008 or earlier	14.1 (0.6)	15.8 (0.7)	15.0 (0.5)
Hypertension	50.0 (1.1)	50.1 (1.2)	50.1 (0.8)
Heart disease**	18.0 (0.7)	14.9 (0.8)	16.5 (0.5)
Stroke	4.4 (0.4)	3.7 (0.4)	4.0 (0.3)
Arthritis*	35.6 (1.2)	51.6 (0.9)	43.7 (0.9)
Lung disease	6.0 (0.5)	7.1 (0.5)	6.6 (0.4)
Cancer***	10.0 (0.6)	11.7 (0.6)	10.9 (0.5)
Emotional/psychiatric problem*	9.5 (0.7)	17.0 (0.8)	13.3 (0.5)
Depression (ever)*	11.5 (0.7)	21.7 (0.9)	16.6 (0.5)
Pain*	24.0 (0.9)	30.1 (0.9)	27.1 (0.7)
Urinary incontinence*	7.1 (0.5)	24.8 (1.1)	16.0 (0.7)
BMI (mean, SE)	29.4 (0.1)	29.0 (0.1)	29.2 (0.9)
Overweight*	43.7 (1.0)	30.7 (0.9)	37.2 (0.6)
Obese	36.9 (0.9)	38.2 (0.9)	37.6 (0.7)

Percentages and standard errors weighted for complex sample design. Differences between gender assessed by Rao-Scott chi-square test for categorical variables and t-tests for continuous variables. *$p \leq 0.001$; ** $p \leq 0.01$, ***$p \leq 0.05$.

Table 3.2. Development of chronic sleep disturbances within 4 years by gender and diabetic status at baseline.

	Men (n=3727)			Women (n=4288)		
	No Diabetes	**New diabetes**	**Diabetes 2+ years**	**No Diabetes**	**New diabetes**	**Diabetes 2+ years**
	n=2888	**n=177**	**n=662**	**n=3371**	**n=145**	**n=772**
	% (SE)	**% (SE)**	**% (SE)**	**% (SE)**	**% (SE)**	**% (SE)**
Trouble Most of the Time						
Falling Asleep	5.4 (0.5)	8.6 (3.5)	6.3 (1.0)	8.1 (0.6)	18.4 (5.8)	9.8 (1.3)
Staying Asleep	14.8 (1.0)	15.3 (3.6)	15.6 (1.8)	15.3 (0.8)	19.5 (4.5)	19.2 (1.8)
One or More Chronic Sleep Disturbance	16.7 (1.0)	19.3 (3.9)	17.1 (1.7)	18.6 (0.9)	29.1 (5.7)	21.3 (1.9)

Diabetes based on self-report of having received a diagnosis from a medical professional or HbA1c >6.5mg/dl.
No diabetes: no diagnosis and HbA1c<6.5; New diabetes: Self-report of diagnosis in 2009 or later or HbA1c in 2010 >6.5mg/dl; Diabetes 2+ years: Self-report of diagnosis prior to 2009.

Sleep disturbances reported in 2014 interview: trouble falling asleep, trouble waking up and not falling back asleep, trouble waking up too early.

Percentages and standard errors weighted for complex sample design. *Rao-Scott Chi-square test of significance within gender, $p<0.05$.

Table 3.3 Odds of developing a chronic sleep disturbances within four years of being diagnosed with diabetes.

	Men OR (95% CI)	Women OR (95% CI)
Logistic Regression Models		
Unadjusted	1.19 (0.71-1.99)	**1.80 (1.01-3.20)**
Adjusted-1	1.21 (0.71-2.04)	1.77 (0.98-3.20)
Adjusted-2	1.16 (0.69-1.90)	1.63 (0.86-3.09)

Model Adjusted-1: adjusted for demographic characteristics age, education, race/ethnicity, and prevalent diabetes.

Model Adjusted-2: adjusted for model 1 variables plus lifestyle and health variables including marital status, employment status, physical activity, smoking, alcohol consumption, obesity, hypertension, chronic pain, arthritis,
ever had depression, incontinence.

Supplemental Table 3.1s. Logistic regression models of the odds of developing a chronic sleep disturbance within 4 years by baseline diabetic status and gender.

Odds Ratios and 95% Confidence Intervals from unadjusted and adjusted logistic regression models.

Men (n=3,727)	1. Unadjusted	2. Adjusted age, race/ethnicity, education	3. Adjusted Model 2 + lifestyle & health conditions	Women (n=4,288)	1. Unadjusted	2. Adjusted age, race/ethnicity, education	3.Adjusted Model 2 + lifestyle & health conditions
New diabetes	1.19 (0.71-1.99)	1.21 (0.71-2.04)	1.16 (0.69-1.93)	New diabetes	**1.80 (1.01-3.20)**	1.77 (0.98-3.20)	1.63 (0.86-3.09)
Diabetes 2+ years	1.02 (0.80-1.32)	1.00 (0.78-1.29)	0.93 (0.70-1.23)	Diabetes 2+ years	1.18 (0.93-1.51)	1.18 (0.92-1.52)	1.05 (0.81-1.36)
Age 60-69		1.11 (0.84-1.46)	1.04 (0.80-1.36)	Age 60-69		1.12 (0.86-1.46)	0.91 (0.69-1.19)
Age 70-79		1.18 (0.91-1.52)	1.09 (0.81-1.46)	Age 70-79		0.94 (0.71-1.25)	**0.70 (0.49-0.99)**
Age 80+		1.10 (0.75-1.64)	1.01 (0.64-1.59)	Age 80+		0.81 (0.58-1.13)	**0.59 (0.39-0.91)**
Black		1.00 (0.70-1.41)	1.00 (0.72-1.39)	Black		**0.78 (0.61-0.99)**	**0.77 (0.60-0.98)**
Hispanic		1.03 (0.71-1.48)	1.10 (0.75-1.60)	Hispanic		0.75 (0.56-1.00)	0.78 (0.57-1.05)
Education: < HS		1.19 (0.87-1.63)	1.13 (0.82-1.57)	Education: < HS		**1.28 (1.02-1.60)**	1.16 (0.91-1.47)
Education: some college		1.05 (0.74-1.48)	1.04 (0.73-1.48)	Education: some college		1.05 (0.82-1.35)	1.11 (0.88-1.42)
Education: college degree		1.25 (0.90-1.73)	1.37 (0.97-1.92)	Education: college degree		0.83 (0.68-1.02)	0.96 (0.78-1.19)
Currently married			1.06 (0.81-1.38)	Currently married			0.99 (0.78-1.25)
Currently working			**0.75 (0.60-0.95)**	Currently working			**0.68 (0.53-0.87)**
Overweight			1.17 (0.84-1.64)	Overweight			1.20 (0.89-1.63)
Obese			1.37 (0.98-1.92)	Obese			1.17 (0.89-1.55)
Physical activity			0.92 (0.70-1.21)	Physical activity			0.94 (0.75-1.18)
Alcohol use			1.24 (0.97-1.58)	Alcohol use			1.03 (0.79-1.34)
Current smoker			1.18 (0.86-1.62)	Current smoker			1.20 (0.87-1.64)
Hypertension			0.85 (0.66-1.11)	Hypertension			0.94 (0.76-1.16)
Heart disease			0.98 (0.70-1.39)	Heart disease			1.05 (0.77-1.43)
Pain			**1.39 (1.04-1.85)**	Pain			**1.50 (1.17-1.94)**
Depression (ever)			**1.56 (1.08-2.26)**	Depression (ever)			**1.31 (1.06-1.63)**
Incontinence			1.20 (0.77-1.87)	Incontinence			**1.34 (1.05-1.71)**
Arthritis			1.16 (0.91-1.48)	Arthritis			**1.35 (1.11-1.65)**

Reference groups: 50-59 years of age, Non-Hispanic white, high school education, healthy BMI <25. All analysis adjusted for complex sample design and age.
Bolded values are statistically significant
Models adjusted for variables shown
Diabetes based on self-report of having received a diagnosis from a medical professional or HbA1c >6.5mg/dl.
No diabetes: no diagnosis and HbA1c<6.5; New diabetes: Self-report of diagnosis in 2009 or later or HbA1c in 2010 >6.5mg/dl; Diabetes 2+ years: Self-report of diagnosis prior to 2009.
Sleep disturbances reported in 2014 interview: trouble falling asleep, trouble waking up and not falling back asleep, trouble waking up too early.

Chapter 4 Comorbidity of diabetes and chronic sleep disturbances and consumption of a Mediterranean-style diet.

Abstract

Objective: This study assessed whether comorbidity of diabetes and chronic sleep disturbances was associated with less healthy dietary consumption, defined as a Mediterranean-style Diet, compared to adults with only one or neither of the conditions.

Research Design and Methods: Participants were selected from the Health and Retirement Study (HRS). Diabetes status and chronic sleep disturbances were assessed during the 2010 interview. Participants were categorized into one of four groups: no sleep disturbances or diabetes, sleep disturbances, diabetes, or sleep disturbances and diabetes. In 2013, 7,423 participants completed a food frequency questionnaire by mail from which the alternative Mediterranean Diet (aMedDiet) score was calculated. Logistic regression was used to assess the main effects of chronic sleep disturbances and diabetes on aMedDiet as well as the interaction of chronic sleep disturbances and diabetes on dietary intake. The odds of consuming an aMedDiet in the highest versus the lowest quartile was estimated based on comorbidity of diabetes and chronic sleep disturbances. Models were stratified by gender. A sensitivity analysis was conducted to assess the linear relationship between diabetes status, chronic sleep disturbances and the aMedDiet score among the full study population.

Results: After adjusting for age and caloric intake, men with diabetes were more likely to consume an aMedDiet in the highest quartile (OR 1.45; 95% CI 1.11-1.91) than men with neither

chronic sleep disturbances nor diabetes. The magnitude of the association increased after adjustment for additional demographic and health variables (OR 1.70, 95% CI 1.25-2.29). Women with sleep disturbances were less likely to consume an aMedDiet than those without sleep disturbances. The reduction in the odds of consuming an aMedDiet was greatest among women with comorbidity of the two conditions (OR 0.53, 95% CI 0.37-0.77) yet was also significant among those with chronic sleep disturbances alone (OR sleep disturbances 0.71, 95% CI 0.56-0.90). The results in women were attenuated after multivariate adjustment. The direction of the associations was the same using linear regression.

Conclusion: Chronic sleep disturbances are associated with reduced healthy dietary intake in adults with diabetes. Differences in the association between diabetes and dietary intake are observed between men and women, as well as in the joint association of diabetes and chronic sleep disturbances and dietary intake.

Key words cohort, sleep disturbance, sleep quality, diabetes, dietary intake, nutrition, Mediterranean Diet, comorbidity

Introduction

The prevalence of diagnosed diabetes among adults in the United States nearly tripled between 2008 and 2012 with the greatest increases among women, those with a high school education, older adults and Hispanic adults (1-3). The increase in type II diabetes brings with it additional population-based and individual costs and considerations. At the individual level, access to adequate and routine medical care, access to affordable medication and the ability to maintain one's employment and lifestyle are all important. At the population-level, the increased prevalence of diabetes can lead to an increased population burden related to medical care and prescription coverage among the un- and under-insured, lost days of work and productivity, as well as increased demands on caregivers.

Glycemic control is the primary goal of individuals with diabetes. This is accomplished through a combination of healthy lifestyle choices as well as medication. A key component of a healthy lifestyle is consuming a diet that provides food sources and nutrients that maintain glycemic control. The Mediterranean diet has been identified as a plant-based dietary pattern that is associated with healthy aging, improved glycemic control and reduced insulin resistance in healthy populations, as well as in those with cardiovascular disease including hypertension and diabetes (4-5). Plant-based diets that are naturally high in polyphenols and low in saturated fats are also associated with decreased inflammation (6-9). Recent evidence also supports the role of the Mediterranean Diet in improving the gut microbiome thereby reducing inflammation and potentially improving glycemic control as well (10,11). The Mediterranean diet is considered a healthy diet for those with diabetes and meets the key dietary criteria outlined by the American Diabetes Association as it is naturally low in saturated fats, highly processed foods and refined carbohydrates.

Chronic sleep deprivation, as well as poor sleep quality, has been linked to metabolic disturbances, including increased caloric intake and cravings for refined carbohydrates (12,13). While such metabolic disturbances are not healthy for the population in general, these disturbances can lead to deleterious outcomes among individuals with diabetes whose daily goal is to maintain glycemic control. Numerous studies have shown an increased prevalence of sleep disruptions among individuals with diabetes (14-24). However, little is known about the association between chronic sleep disturbances and dietary intake specifically among adults with diabetes. Given the importance of a healthy dietary intake among those with diabetes, a better understanding of this potential relationship could allow for improved care and treatment, thus improving the quality of life and potential outcomes of adults with diabetes.

The goals of this study were to determine whether older adults with diabetes and chronic sleep disturbances were less likely to consume a healthy diet, as measured by the alternate Mediterranean Diet score, than those without diabetes or chronic sleep disturbances. Differences in the association were assessed by gender as well as race and ethnicity given the increased rates of chronic sleep disturbances among women compared to men and increased rates of diabetes among Black and Hispanic adults.

Research Design and Methods

Participants were drawn from the Health and Retirement Study. The Health and Retirement Study is a national, longitudinal study representative of the U.S. population age 51 and older. The study began in 1992 and includes a new cohort of individuals age 50-55 every six years in order to maintain representation of the U.S. population in this age group as well as the older age groups as the study sample ages. The study is designed to measure the health and wealth of the U.S. population pre-retirement and as the population ages and retires. The study has been described in detail previously (25). Panel participants are interviewed every two years by phone or in person. The complex sample design, including oversamples of Black and Hispanic participants, allows for broad population-based inferences (26). The Health and Retirement Study is approved by the University of Michigan Institutional Review Board. The Health and Retirement Study (HRS) is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. The NIA provided funding for the 2013 HCNS as well (27).

Study Sample

Participants for the current study were those that completed an interview for the Health and Retirement Study (HRS) in 2010 as well as the Health Care and Nutrition Study (HCNS) in 2013 (n=8,035). The HCNS was a self-administered survey mailed to a subset of HRS panel participants and included questions on health care access and utilization, food security and availability as well as a previously validated Food Frequency Questionnaire (FFQ) (28-30). Those who reported daily caloric intake levels, calculated from the HCNS FFQ, above or below extreme values were excluded (<500 or >8000 calories/day; n=342). Cases were excluded if they did not provide a response to questions on sleep disturbances (n=342) during their 2010

interview. A total of 7,423 participants (4,429 women, 2,994 men) were included in the current study ranging in age from 52-96 years.

Measures

Self-reported measures of demographic characteristics and health status, including sleep quality measures and diabetic status, were collected at each two-year period.

Chronic sleep disturbances

Participants were asked three questions related to the frequency of sleep disturbances. The questions assessed difficulty initiating and maintaining sleep. The questions were: "How often do you have trouble falling asleep?", "How often do you have trouble with waking up during the night?" and "How often do you have trouble with waking up too early and not being able to fall asleep again?". Three response options were read aloud to the participant: Most of the time, Sometimes, Rarely or Never. Responses to the three questions were dichotomized to 1=Yes (Most of the time) or 0=No (Sometimes, rarely or never) in order to capture ongoing, chronic sleep disturbances. The number of sleep disturbance problems endorsed was calculated by summing the response to these three questions. A composite variable was created to categorize those who reported that they had one or more chronic sleep disturbance most of the time versus those who did not have a chronic sleep disturbance.

Diabetes

A participant was considered as having diabetes if they reported that a doctor or other medical professional had told them that they had diabetes during their 2012 interview or prior. Hemoglobin A1C values from the two most recent interviews (2010 and 2012) were evaluated for participants who reported that they had never been diagnosed with diabetes. A result of 6.5mg/dL or greater, assayed from a non-fasting dried blood spot collected in the home at the

time of the interview was considered positive for diabetes (1). Collection and processing procedures for the dried blood spots have been described previously (30).

Comorbid diabetes and chronic sleep disturbances

Respondents were categorized into 4 groups to determine the comorbidity of diabetes and chronic sleep disturbances: 1) those who did not report either chronic sleep conditions or a diagnosis of diabetes, 2) those who reported chronic sleep disturbances but no diagnosis of diabetes, 3) those who did not report a chronic sleep disturbance but had been previously told by a doctor or other health care professional that they had diabetes and, 4) those who reported both a chronic sleep disturbance and a previous diagnosis of diabetes. Both self-reported diabetes and a HgA1c >6.5mg/dL were considered to be positive for diabetes.

Mediterranean Diet Score

Mediterranean Diet intake was determined using dietary intake information from the food frequency questionnaire (FFQ) included in the 2013 HCNS. The FFQ was previously validated as the Harvard Food Frequency Questionnaire (28-30). The Alternate Mediterranean Diet score (aMedDiet)was calculated (4, 31). The aMedDiet includes 9 components, each scored 0 or 1. The scores are summed with the total aMedDiet score ranging from 0 to 9, with 0 representing the lowest consumption and 9 the highest consumption of a Mediterranean Diet. The aMedDiet score was calculated both by assessing gender-specific median values of daily fruit, vegetable, whole-grain, red/processed meats, alcohol, nuts, legumes, fish and the ratio of monounsaturated fats to saturated fats as well as a score for the full study population. A score of 1 is given to intake values above the gender-specific median for all items with the exception of alcohol and red meat consumption. One point is given for moderate alcohol intake (.5-1.5 drinks per day for women, .5-2 drinks per day for men). Less than moderate alcohol consumption is scored zero.

Consumption below the median intake value for red meat is scored 1 whereas intake daily consumption of red or processed meats at the median level or higher is scored 0, thus recognizing the health risks associated with the intake of red and processed meats. Intake of potatoes, poultry and full-fat dairy are excluded from the aMedDiet, all of which were included in previous Mediterranean Diet scores. A ratio of healthy to unhealthy fat intake is assessed in the aMedDiet whereas the original Mediterranean Diet score included olive oil intake. The dietary components and scoring mechanisms for the current study population are shown in supplemental table 1.

Covariates: Demographic, health behaviors, health conditions

Demographic variables assessed included self-reported age, gender, years of education, race and ethnicity. Respondents were categorized as Hispanic, non-Hispanic Black, and non-Hispanic white/other based on responses to two separate questions on Hispanic ethnicity and race. Years of education was used as a measure of socio-economic status and was categorized as less than high school, high school graduate, some college and college graduate. Marital and employment status were assessed in 2010 and coded as dichotomous variables. Marital status was coded as currently married versus not married (including never married, separated/divorced and widowed). Work status was coded as currently working or not working.

Health behaviors of interest included self-reported measures of physical activity and current smoking status. Participants who reported engaging in moderate or vigorous physical activity at least once a week on average were considered to be physically active. Respondents who reported that they currently smoke cigarettes were categorized as smokers.

Respondents were asked about the presence of chronic diseases at the time of the interview ("Has a doctor or other medical professional ever told you that you have…"). Self-

reported previous diagnosis of hypertension, heart disease, previous heart attack and depression were dichotomized based on either having the condition or not having the condition. Body mass index (BMI) was calculated based on self-reported height and weight in 2010. For those respondents who did not provide their height or weight in 2010, current height and weight were imputed from the previous interview. A correction factor was applied to weight based on the mean weight increase in the two years. Weight was recorded in pounds to the nearest half pound. Height was measured in inches to the nearest half inch. Body mass index was calculated as (weight/ height^2) x 703. BMI was then categorized as normal weight (up to 24.9), overweight (25-29.9) and obese (30 or greater) (33).

Statistical Analysis

A descriptive analysis of all demographic, health behaviors and conditions was assessed by gender, as well as by the exposure and the outcome. Mean values of continuous variables were compared using analysis of variance. Chi-square tests were utilized to assess the associations of categorical variables. The mean Mediterranean diet score was assessed by gender and comorbidity of chronic sleep disturbances and diabetes. Dietary intake scores for each of the nine Mediterranean Diet components were assessed by gender and both the main effects of chronic sleep disturbances and diabetes, as well as the comorbidity of both chronic sleep disturbances and diabetes, to determine the foods with the greatest difference in intake between subgroups. Gender-specific quartiles of Mediterranean Diet intake were created based on the aMedDiet score. Logistic regression was used to assess the odds of consuming a Mediterranean diet by comparing the highest intake quartile with the lowest. In women, a score of 2 or lower was categorized as the lowest quartile and a score of 6 or higher was considered the highest intake quartile. In men, the lowest quartile was based on a score of 3 or less. The highest quartile

of intake for men was the same as the cut-off for women (6-9). Separate models were calculated by gender to assess the odds of consuming a high aMedDiet in the presence or absence of chronic sleep disturbances and diabetes (four groups of comorbidity of the two conditions described previously). First, the main effects of diabetes and chronic sleep disturbances were assessed in separate multivariate logistic regression models. Next, the joint association of chronic sleep disturbances and diabetes was assessed by first adjusting for age and caloric intake as well as the complex sample design. Additional multivariate logistic regression models were estimated adjusting for age, caloric intake, demographic, behavior and health characteristics including race/ethnicity, education, employment status, marital status, hypertension, depression, smoking, physical activity and obesity (categorized as normal weight, overweight or obese). As a sensitivity analysis, the aMedDiet score was calculated for the full study population and multivariate linear regression was used to assess the relationship between diabetes and chronic sleep disturbances with the score as the outcome variable. All analyses were weighted for the complex sample design. All statistical tests were two-sided at a significance level of 0.05. SAS v9.4 (SAS Institute, Inc., Cary, NC) was used for data analysis.

Results

Demographic, lifestyle and health characteristics of the study population are shown in supplemental table 4.S1. The mean age of the population was 65 years of age (65.2 men, 64.9 women). Close to one-third of men and women reported suffering from a chronic sleep disturbance (31.3% of men and 35.2% of women, p=0.001). The most common sleep disturbance for both genders was waking up at night and not being able to fall back asleep. Approximately a quarter of men and women had previously been told by a doctor that they had diabetes or had an HbA1c result indicative of diabetes (26.7% men, 24.2% women, p=0.015). In assessing the

comorbidity of diabetes and chronic sleep disturbances, just over half of all men and women did not report the presence of chronic sleep disturbances or diabetes (51%). Slightly more women than men had sleep disturbances but not diabetes (25.0% vs 22.3%, respectively). The presence of diabetes without a chronic sleep disturbance was more common in men than women (17.7% vs. 13.9%, respectively). Women were more likely to have both chronic sleep disturbances and diabetes than men (10.2% vs. 9.0%, respectively). The differences by gender were statistically significant ($p<0.001$). The average Mediterranean Diet score was 4.0 in men and 3.9 in women and ranged from 0 to 9 in both men and women. Total daily caloric intake was higher in men than women (2013 vs. 1797 kcal/day, $p<0.001$).

In men, the average aMedDiet score was highest in those with diabetes and no sleep disturbances (4.24±1.88). In women, the aMedDiet was highest among those without sleep disturbances or diabetes (4.06±2.09). The aMedDiet score was lower among those with chronic sleep disturbances than among those without sleep disturbances and those without diabetes for both men and women. The cormorbidity group with the lowest average aMedDiet score in both men and women was the group with both chronic sleep disturbances and diabetes (men: 3.87±1.90; women: 3.63±1.82). Differences within and between gender were statistically significant (shown in Figure 4.1a). A similar pattern was observed by gender and comorbid group when the full study population score was used. Median scores were slightly higher for all components but the increased aMedDiet among men with diabetes was observed whereas women without diabetes or chronic sleep disturbances had the highest aMedDiet score. The median aMedDiet score was lowest for women with diabetes and chronic sleep disturbances and for men who either had chronic sleep disturbances alone or reported chronic sleep disturbances as well as diabetes (Figure 4.1b).

Variation in consumption of the nine aMedDiet components by comorbidity group was observed in men and women. Men with diabetes and sleep disturbances were less likely to consume daily servings above the median (i.e. receive a score of 1 for the component) of fruits, vegetables, whole grains, nuts and fish than those with diabetes and no sleep disturbances. Men with diabetes and sleep disturbances were also more likely to consume higher quantities of red/processed meats, less likely to consume moderate alcohol intake, and had a lower MUFA:SFA ratio. A similar pattern is observed in women with the exception of consumption of alcohol, nuts and fish which is higher among diabetics with sleep disturbances and diabetes than those without sleep disturbances. In both men and women, the two groups with chronic sleep disturbances have lower intake of the aMedDiet components than those without chronic sleep disturbances (table 4.1).

Significant differences in demographic and health characteristics for those in the highest versus the lowest quartile of aMedDiet score were observed by gender (table 4.2). Men in the highest quartile of intake were more likely to be Hispanic, have a college degree, be currently working, engage in weekly physical activity and not smoke. Men in the highest quartile were also less likely to have a chronic sleep disturbance, with or without diabetes, than those in the lowest quartile of intake. The differences among women in the highest quartile varied with those in the lowest quartile to an even greater degree as significant differences in self-reported health conditions were observed as well. In both men and women, those in the highest quartile of aMedDiet intake consumed significantly more calories on a daily basis than those in the lowest quartile.

The main effects of diabetes and chronic sleep disturbances were assessed using multivariate logistic regression by gender. Men with diabetes alone were more likely to consume

an aMedDiet in the highest quartile compared to those without diabetes (OR 1.30, 95% CI 0.95-1.77) whereas men with chronic sleep disturbances were less likely to consume an aMedDiet in the highest quartile (OR 0.84, 95% CI 0.62-1.14). Women with diabetes were just as likely as those without diabetes to consume an aMedDiet in the highest quartile (OR 1.00, 95% CI 0.66-1.50) whereas those with chronic sleep disturbances were less likely to consume an aMedDiet in the highest quartile (OR 0.86, 95% CI 0.67-1.09). The main effects were not statistically significant (data not shown).

After adjusting for age and caloric intake, men with diabetes but no chronic sleep disturbances were 45% more likely to be in the highest quartile of aMedDiet intake than those without diabetes or chronic sleep disturbances (OR 1.45, 95% CI 1.11-1.91). However, although not statistically significant, those with sleep disturbances were less likely than those without to be in the highest quartile of aMedDiet intake. After multivariate adjustment, the association between diabetes and consumption of an aMedDiet was increased (OR 1.70, 95% CI 1.25-2.29). The odds of being in the highest quartile of aMedDiet intake was similar for those with sleep disturbances, either with or without diabetes, as compared to those without chronic disturbances of sleep or diabetes. A somewhat different pattern was observed in women. After adjusting for age and caloric intake in women, women with sleep disturbances, with or without diabetes, were significantly less likely to be in the highest quartile of aMedDiet intake than those without either chronic sleep disturbances or diabetes. Women with sleep disturbances alone were 71% less likely to consume an aMedDiet (OR 0.71, 95% CI 0.56-0.90) whereas those with both diabetes and chronic sleep disturbances were 53% less likely to be in the highest quartile of aMedDiet intake compared to those with neither chronic sleep disturbances nor diabetes (OR 0.53, 95% CI 0.37-0.77). These results were no longer significant after multivariate adjustment (Table 4.3).

The weighted median values used for creating the gender-specific scores and full study population score is shown in supplemental table 4.S2. When assessing the relationship between diabetes and chronic sleep disturbances as a sensitivity analysis in the full study population using multivariate linear regression, those with diabetes and no sleep disturbances have a 0.22 increased aMedDiet score (95% CI 0.06, 0.37) whereas those with both diabetes and chronic sleep disturbances have a -0.14 decreased aMedDiet score (95% CI -0.25, -0.03).

Conclusions

The results of our study indicate that men with diabetes are more likely to consume a healthy diet, as assessed by the alternate Mediterranean Diet, *unless* they also have a chronic sleep condition. Conversely, we found that women with diabetes are less likely to consume a healthy diet, *especially* in the presence of chronic sleep disturbances. Chronic sleep disturbances appear to diminish the association between diabetes and healthy dietary intake. Our study provides new evidence that chronic sleep disturbances may be antagonistic, or have a negative association, with healthy dietary consumption in adults with diabetes. This finding is of both public health and clinical importance given that our study population consisted of individuals with a chronic condition, diabetes, for whom a healthy diet is of vital importance.

The differences by gender may be attributed to differences in the foods men and women consume when affected by chronic sleep disturbances. Individuals with chronic sleep disturbances tend to exchange consumption of healthier dietary components, such as vegetables and lean proteins, for those offering less healthy benefits, such as carbohydrates (33, 34). In our study population, women with diabetes reported higher levels of consumption of fruits, whole grains and red/processed meats than women with neither diabetes nor chronic sleep disturbances. Women with diabetes consumed less vegetables, nuts, legumes, fish and moderate alcohol.

Conversely, men with diabetes consumed the highest rates of all aMedDiet food groups with the exception of red/processed meats and moderate alcohol consumption. Thus, men with diabetes consumed a diet more typical of a Mediterranean diet than women. Additionally, greater declines in consumption rates were reported in women with sleep disturbances compared to those with neither sleep disturbances nor diabetes, than in men. In our study population, men with diabetes consumed fewer calories per day compared to those without diabetes or chronic sleep problems. In women, no difference in caloric intake was observed among women with or without diabetes. Thus, it appears that women may not adjust their diet in the same way as men with diabetes. Differences in treatment and adherence by gender can be considered as possible explanations for our findings (35-37). In terms of treatment, it is possible that men are more likely to receive nutritional counseling than women, potentially due to gender stereotypes surrounding who plans, shops for and prepares meals. Conversely, it is also possible that there are differences in perceived treatment with women being more likely to rely on the benefits of pharmaceutical treatment rather than changing lifestyle factors that they can influence. A review of behavioral factors related to glycemic control among adults with diabetes found that adherence to dietary requirements was correlated with increased self-efficacy and coping skills (38). If women with diabetes experience lower levels of self-efficacy than men with diabetes, possibly feeling less in control of their disease, adherence to dietary intake guidelines could be affected. Halali and colleagues found that situational barriers and difficulty resisting temptation, as well as stress-related eating disorders were the two primary factors that affected dietary adherence in diabetic patients (39). While prior studies on dietary adherence among adults with diabetes were not able to determine differences by gender, it is possible that these barriers exist to a greater degree in women than men. The role of obesity should be considered as well. Obesity may be a confounder

as well as a mediator in the relationship between sleep and diet. In our study population, mean BMI increased in a linear direction for men and women based on comorbidity of diabetes and chronic sleep disturbances. In women, the mean BMI was the same in women with diabetes, with or without sleep disturbances, and the difference with those without chronic conditions is greater in women than among men. Additionally, both men and women with diabetes and sleep disturbances are more likely to be obese. Interaction terms for comorbidity and obesity as well as race-ethnicity and obesity were tested in our regression models. While the terms were not significant for women, obesity appears to confound the relationship between comorbidity status and dietary adherence in men.

The prevalence of chronic sleep disturbances in our study population is similar to that reported in other population-based studies with approximately one-third of women and men reporting chronic sleep disturbances. However, these rates were higher among adults with diabetes than those without diabetes, with women disproportionately affected by chronic sleep disturbances: 30% of men without diabetes and 34% of men with diabetes reported chronic sleep disturbances whereas 33% of women without diabetes and 42% of women with diabetes reported chronic sleep disturbances. While it is possible that the lower rate of chronic sleep disturbances in men is due to underreporting, we would not expect underreporting to be differential with respect to dietary intake.

The aMedDiet score is based on population-specific intake of key dietary components representing the Mediterranean diet. Median values are gender-specific as they are based on daily servings and daily caloric intake is typically significantly higher in men than women. The aMedDiet was previously calculated for participants of the Nurses' Health Study (NHS) to determine whether differences existed between healthy agers and usual agers (those who

developed chronic conditions. The NHS study population was free of chronic diseases and ranged in age from late 50s to early 60s (4). Our study population consumed approximately 150 calories per day more than the usual agers and 200 calories more than healthy agers in the NHS. The average aMedDiet score among women in our study population was 4.0 compared to 4.5 in healthy agers and 4.3 in usual agers in the NHS study. The aMedDiet was used by DeKoning and colleagues to determine the risk of developing diabetes among participants in the Health Professionals Follow-Up Study (HPFS). Participants who were free of cardiovascular disease, type 2 diabetes and cancer were included. Participants in the lowest quartile of aMedDiet in the HPFS consumed on average 50 kcal more per day than our study population in the lowest quartile yet approximately 150 kcal less per day in highest quartile. On average, the BMI of men in the highest quartile in the HPFS was within normal range whereas the men in our study had a BMI indicative of obesity. The somewhat less healthy dietary profile in our study population compared to NHS and HPHS participants could be due to the differences in study populations. Our population is representative of the U.S. population whereas NHS and HPFS is a study of health professionals, free of chronic diseases, who may have been more informed of healthy dietary choices than the general population. Another explanation is the time difference in assessing diet between our study and the other two. Over the last thirty years, vast changes in the U.S. dietary pattern and food supply have occurred as well as dramatic increases in obesity rates. Both men and women in our study population had a less healthy dietary profile than participants in the NHS and HPFS.

A strength of this study is the large, nationally representative sample that allow for analysis stratified by gender as well as comparisons of minority racial and ethnic subgroups. Limitations include the observational nature of the study which does not support causal

inference, despite the associations detected. Additionally, the exposure and the outcome variables are based on self-report and limited to those who provided the information, both of which could lead to potential sources of measurement error. Another limitation is the gender-specific creation of the scores based on median intake within gender leading to composite scores which are not entirely comparable. However, including caloric intake in the regression analyses adjusts for variation due to higher daily consumption. Another limitation of the study is the lack of information on sleep apnea thus not allowing for the determination of the degree to which sleep disturbances are actually due to sleep apnea.

Dietary intake is a modifiable risk factor that can reduce the impact of diabetes on the development of additional cardiovascular diseases. Evidence that sleep disturbances among individuals with diabetes reduces diet quality is important to take into account for both prevention and treatment purposes. Two primary areas of focus are to be highlighted with these findings: the need to ensure that those with diabetes continue to consume a healthy diet if they are already doing so, and the need to focus on chronic sleep disturbances as a potential source of reducing dietary quality in those with diabetes. Given the global impact at the population and individual level of increasing rates of diabetes, adding a piece of fruit, an extra serving of vegetables, a handful of nuts, or a splash of olive oil to one's daily diet is a viable option to improving dietary consumption among adults with diabetes. However, economic barriers may reduce the current ability for older adults to adopt this behavior change and consume a Mediterranean-style diet. Providing low cost, affordable access to healthy foods is a key area for intervention. Additionally, the impact of chronic sleep disturbances should not be ignored in the on-going health and maintenance of those with chronic conditions such as diabetes. Chronic sleep disturbances should be assessed among older patients with diabetes by both clinicians as

well as nutritionists. Future studies are needed to confirm this relationship as well as to determine whether the glycemic control is reduced among those with diabetes and chronic sleep disturbances compared to those without chronic sleep disturbances.

References

1. Geiss L, Wang J, Cheng Y et al. Prevalence and Incidence Trends for Diagnosed Diabetes Among Adults Aged 20 to 79 Years, United States, 1980-2012. JAMA. 2014;312(12):1218-1226.

2. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium, International Diabetes Federation, 2013.

3. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27: 1047-1053.

4. Samieri C, Sun Q, Townsend M et al. The relation of midlife diet to healthy aging: a cohort study. Annals of Internal Medicine. 2013. 159(9):584-591.

5. DeKoning L, Chiuve S, Fung T, et al. Diet-quality scores and the risk of type 2 diabetes in men. Diabetes Care. 2011. 34(1150-1156).

6. Casas-Agustench P, Lopez-Uriarte P, Bullo M, Ros E, Cabre-Vila J, Salas-Salvado J. Effects on one serving of mixed nuts on serum lipids, insulin resistance and inflammatory markers in patients with the metabolic syndrome. Nutrition, Metabolism and Cardiovascular Diseases. 2011. 21:126-135;

7. Guasch-Ferre M, Becerra-Tomas N, Ruiz-Canela M, et al. Total and subtypes of dietary fat intake and risk of type 2 diabetes mellitus in the prevencion con dieta Meditarranea (PREDIMED) study. American Journal of Clinical Nutrition. 2017. 105:723-35.

8. Santangelo C, Filesi C, Vari R, et al. Consumption of extra-virgin olive oil rich in phenolic compounds improves metabolic control in patients with type 2 diabetes mellitus: a possible involvement of reduced levels of circulating visfatin. Journal of Endocrinology Investigation. 2016. 39:1295-1301.

9. Jacobs S, Boushey C, Franke A, et al. A priori-defined diet quality indices, biomarkers and risk for type 2 diabetes in five ethnic groups: the Multiethnic Cohort. British Journal of Nutrition. 2017. 118:312-320.

10. Kang I, Buckner T, Shay NF, Gu L, Chung S. Improvements in metabolic health with consumption of ellagic acid and subsequent conversion into urolithins: evidence and mechanisms. Advances in Nutrition. 2016. 15;7(5):961-72.

11. Guasch-Ferre M, Merino J, Sun Q. Dietary polyphenols, Mediterranean diet, prediabetes, and type 2 diabetes: a narrative review of the evidence. Oxidative Medicine and Cellular Longevity. 2017. 1-16.

12. Cappuccio F, Miller M. Sleep and Cardio-Metabolic Disease. Current Cardiology Reports. 2017. 19;19(11):110.

13. Cedernaes J, Schloth HB, Benedict C. Determinants of shortened, disrupted, and mistimed sleep and associated metabolic health consequences in healthy humans. Diabetes 2015 Apr;64(4):1073-80.

14. Kim BK, Kim BS, An SY, Lee MS, Choi YJ, Han SJ, Chung YS, Lee KW, Kim DJ. Sleep duration

and glycemic control in patients with diabetes mellitus: Korea National Health and Nutrition Examination Survey 2007-2010. J Korean Med Sci. 2013 Sep;28(9):1334-9.

15. Ohkuma T, Fujii H, Iwase M, Kikuchi Y, Ogata S, Idewaki Y, Ide H, Doi Y, Hirakawa Y, Nakamura U, Kitazono T. Impact of sleep duration on obesity and the glycemic level in patients with type 2 diabetes: the Fukuoka Diabetes Registry. Diabetes Care. 2013 Mar;36(3):611-7.

16. Larcher S, Benhamou PY, Pépin JL, Borel AL. Sleep habits and diabetes. Diabetes and Metabolism. 2014.

17. Arora T, Taheri S. Sleep Optimization and Diabetes Control: A Review of the Literature. Diabetes Ther (2015) 6:425–468.

18. Knutson K, Ryden A, Mander B, VanCauter E. Role of Sleep Duration and Quality in the Risk and Severity of Type 2 Diabetes Mellitus. Arch Intern Med. 2006;166:1768-1774.

19. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011 Jun;32(12):1484-92.

20. Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes Ann. N.Y. Acad. Sci. 1311 (2014) 151–173.

21. Zhu B, Vincent C, Kapella MC, et al. Sleep disturbance in people with diabetes: A concept analysis. J Clin Nurs. 2017;00:1–12.

22. Narisawa H, Komada Y, Miwa T, Shikuma J, Sakurai M, Odawara M, Inoue Y. Prevalence, symptomatic features, and factors associated with sleep disturbance/insomnia in Japanese patients with type-2 diabetes. Neuropsychiatric Disease and Treatment 2017;13:1873-1880.

23. Johnson S, Thiel D, Al Sayah F, Mundt C, Qiu W, Buman M, Vallance J, JohnsonJ. Objectively measured sleep and health-related quality of life in older adults with type 2 diabetes: a cross-sectional study from the Alberta's Caring for Diabetes Study. Sleep Health 2017;3:102-106.

24. Montag S, Knutson K, Zee P, Goldberger J, Ng J, Kim KY, Carnethon M. Association of sleep characteristics with cardiovascular and metabolic risk factors in a population sample: the Chicago Area Sleep Study. Sleep Health. 2017;3:107-112.

25. Sonnega A, Faul JD, Ofstedal MB et al. Cohort profile: The Health and Retirement Study (HRS). International Journal of Epidemiology. 2014. 43:576-585.

26. Heeringa SG, Connor J. Technical Description of the Health and Retirement Study Sample Design. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 1995.

27. Health and Retirement Study, Cross-wave Tracker, 2006-2014 Core public use dataset, Biomarker data, Health Care and Nutrition Survey 2013. Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740). Ann Arbor, MI, (2017).

28. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantative food frequency questionnaire. American Journal of Epidemiology. 1985. 122(1):51-65.

29. Willett, W. Nutritional Epidemiology. 3. New York and Oxford: Oxford University Press; 2012.

30. Crimmins EM, Guyer H, Langa KM, Ofstedal MB, Wallace RB, Weir DR. Documentation of Physical Measures, Anthropometrics and Blood Pressure in the Health and Retirement Study. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 2008.

31. Trichopolou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. BMJ. 1995. 311(7018):1457-60.

32. Body Mass Index calculator. National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm

33. Cappuccio F, Miller M, Lockley S. Sleep, Health, and Society. From Aetiology to Public Health. 2010. New York. Osford University Press.

34. Campanini M, Guallar Castillon P, Rodriguez-Artalejo F, Lopez-Garcia E. Mediterranean diet and changes in sleep duration and indicators of sleep quality in older adults. Sleep. 2017. 40(3):1-9.

35. Sofi F, Macchi C, Abbate R, Gensini F, Casini A. Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score.

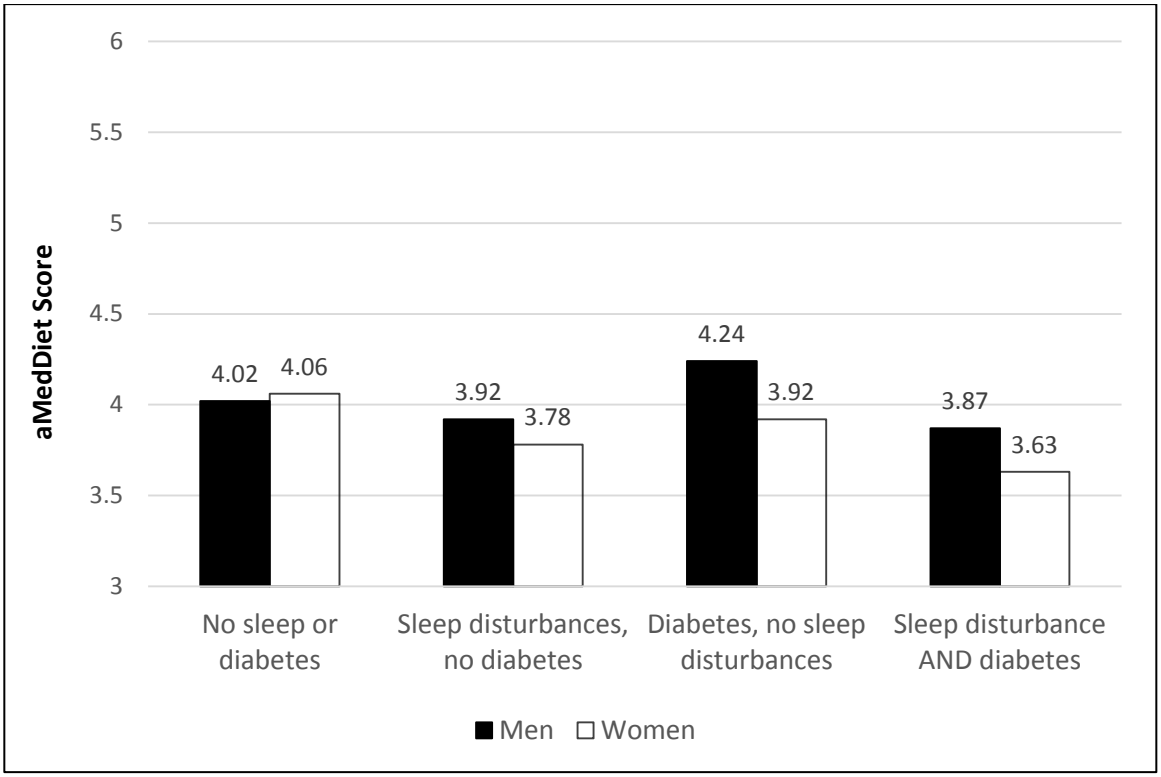
36. Herrera MC, Subhan F, Chan C. Dietary patterns and cardiovascular disease risk in people with type 2 diabetes. Current Obesity Reports. 2017 Oct 23. doi: 10.1007/s13679-017-0284-5.

37. Diez-Espino J, Buil-Cosiales P, Serrano-Martinez M, et al. Adherence to the Mediterranean diet in patients with type 2 diabetes mellitus and HbA1c level. Annals of Nutrition and Metabolism. 2011. 58:74-78.

38. Brown S, Garcia A, Brown A et al. Biobehavioral determinants of glycemic control in type 2 diabetes: a systematic review and meta-analysis. Patient Education and Counseling. 2016. 99(10)1558-1567.

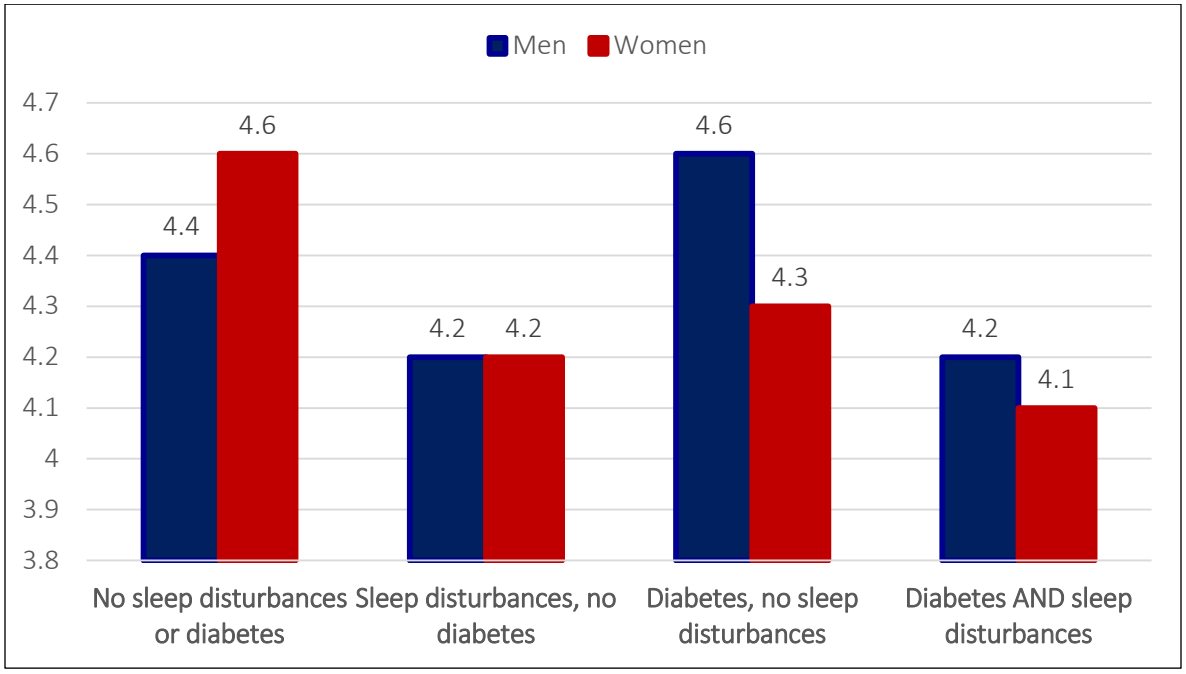
39. Halali F, Mahdavi R, Mobasseri M, Jafarbadi M, Avval S. Perceived barriers to recommended dietary adherence in patients with type 2 diabetes in Iran. Eating Behaviors. 2016. 21:205-210.

Figure 4.1a Average aMedDiet Score Based on Comorbidity of Chronic Sleep Disturbances and Diabetes, by Gender, utilizing the gender-specific median values for the aMedDiet score.



Differences within men: $p<0.05$; Differences within women, $p<0.001$; Differences between men and women $p<0.05$.
aMedDiet: alternate Mediterranean Diet score, range from 0 to 9 based on median intake of 9 dietary components.

Figure 4.2b Average aMedDiet Score Based on Comorbidity of Chronic Sleep Disturbances and Diabetes, by Gender, utilizing the full sample median values for the aMedDiet score.



Differences within men: $p<0.05$; Differences within women, $p<0.001$; Differences between men and women $p<0.05$.
aMedDiet: alternate Mediterranean Diet score, range from 0 to 9 based on median intake of 9 dietary components.

Table 4.1 Percent of the study population that consume above the median value of the aMedDiet dietary components by gender and comorbidity status.*

	Men (n=2994)			
	No sleep disturbances, no diabetes	**Sleep disturbances, no diabetes**	**Diabetes, no sleep disturbances**	**Diabetes AND sleep disturbances**
	n=1527 (51.0%)	n=668 (22.3%)	n=530 (17.7%)	n=269 (9.0%)
aMedDiet Dietary Intake Components	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Fruit, servings per day	753 (49.3)	330 (49.4)	292 (55.1)	127 (47.2)
Vegetables, servings per day	744 (48.7)	336 (50.3)	280 (52.8)	137 (50.9)
Whole grain, servings per day*	730 (47.8)	316 (47.3)	293 (55.3)	142 (52.8)
Red/processed meats, servings per day**	802 (52.5)	305 (45.7)	267 (50.4)	124 (46.1)
Alcohol, 1-2 drinks per day*	574 (37.6)	244 (36.5)	124 (23.4)	58 (21.6)
Nuts, servings per day	756 (49.5)	323 (48.4)	292 (55.1)	135 (50.2)
Legumes, servings per day	500 (32.7)	214 (32.0)	180 (34.0)	91 (33.8)
Fish, servings per day	724 (47.4)	311 (46.6)	255 (48.1)	119 (44.2)
MUFA:SFA ratio*	747 (48.9)	319 (47.8)	303 (57.2)	119 (44.2)
	Women (n=4429)			
	No sleep disturbances, no diabetes	**Sleep disturbances, no diabetes**	**Diabetes, no sleep disturbances**	**Diabetes AND sleep disturbances**
	n=2253 (50.9%)	n=1107 (25.0%)	n=617 (13.9%)	n=452 (10.2%)
aMedDiet Dietary Intake Components	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Fruit, servings per day**	1128 (50.1)	548 (49.5)	333 (54.0)	204 (45.1)
Vegetables, servings per day*	1179 (52.3)	530 (47.9)	316 (51.2)	195 (43.1)
Whole grain, servings per day**	1141 (50.6)	531 (48.0)	344 (55.8)	235 (52.0)
Red/processed meats, servings per day*	1151 (51.1)	521 (47.1)	292 (47.3)	199 (44.0)
Alcohol, 1-2 drinks per day*	545 (24.2)	262 (23.7)	59 (9.6)	48 (10.6)
Nuts, servings per day*	1155 (51.3)	533 (48.1)	273 (44.2)	210 (46.5)
Legumes, servings per day	772 (34.3)	337 (30.4)	209 (33.9)	134 (29.6)
Fish, servings per day	1081 (48.0)	511 (46.2)	287 (46.5)	226 (50.0)
MUFA:SFA ratio**	1172 (52.0)	518 (46.8)	327 (53.0)	221 (48.9)

*p≤0.01; **p≤0.05 All percentages are weighted and standard errors account for the complex sample design.

Table 4.2 Sample characteristics for quartiles 1 and 4 (lowest and highest) of aMedDiet score, by gender.

	Men (n=2994)		Women (n=4429)	
	Quartile 1	**Quartile 4**	**Quartile 1**	**Quartile 4**
	n=1288	n=718	n=1213	n=1030
Demographic Characteristics	**# (%)**	**# (%)**	**# (%)**	**# (%)**
Age (mean yrs, SD)	65.1 (10.5)	64.5 (10.2)	64.5 (11.2)	64.1 (11.2)
Race/Ethnicity* +				
White/other, non-Hisp	973 (75.5)	520 (72.4)	891 (73.5)	702 (68.2)
Black, non-Hisp	180 (14.0)	81 (11.3)	227 (18.7)	163 (15.8)
Hispanic	135 (10.5)	117 (16.3)	95 (7.8)	165 (16.0)
Education*+				
<High school	301 (23.4)	128 (17.8)	288 (23.7)	163 (15.8)
High school	653 (50.7)	273 (38.0)	676 (55.7)	462 (44.9)
Some college	78 (6.1)	36 (5.0)	86 (7.1)	84 (8.2)
College/Professional degree	256 (19.9)	281 (39.1)	163 (13.4)	321 (31.2)
Currently married+	959 (74.5)	547 (76.2)	634 (52.3)	628 (61.0)
Currently working*	514 (39.9)	340 (47.4)	461 (38.0)	425 (41.3)
Health Behaviors				
Weekly moderate or vigorous phys activity*+	864 (67.1)	582 (81.1)	643 (53.0)	773 (75.0)
Current smoker*+	249 (19.3)	58 (8.1)	227 (18.7)	72 (7.0)
Health Conditions				
Diabetes++	325 (25.2)	194 (27.0)	296 (24.4)	209 (20.3)
Hypertension+	760 (59.0)	395 (55.0)	717 (59.1)	499 (48.4)
Heart disease+	339 (26.3)	162 (22.6)	257 (21.2)	148 (14.4)
Heart attack++	131 (10.2)	58 (8.1)	55 (4.5)	27 (2.6)
Depression** +	185 (14.4)	76 (10.6)	313 (25.8)	194 (18.8)
BMI (mean, SD)+	30.4 (5.4)	30.3 (5.2)	31.3 (7.3)	29.3 (6.2)
Normal weight+	175 (13.6)	83 (11.6)	226 (18.6)	259 (25.1)
Overweight	499 (38.7)	300 (41.8)	343 (28.3)	347 (33.7)
Obese	614 (47.7)	335 (46.7)	644 (53.1)	424 (41.2)
Chronic sleep disturbances				
Trouble falling asleep, most of the time*+	161 (12.5)	49 (6.8)	222 (18.3)	118 (11.5)
Trouble waking up at night, most of the time++	317 (24.6)	160 (22.3)	326 (26.9)	224 (21.7)
Trouble waking up too early++	174 (13.5)	85 (11.8)	178 (14.7)	110 10.7)
One or more chronic sleep disturbance*+	430 (33.4)	209 (29.1)	461 (38.0)	309 (30.0)
Comorbidity of diabetes and chronic sleep disturbances ++**				
No diabetes diagnosis/no chronic sleep disturbance	660 (51.2)	367 (51.1)	592 (48.8)	585 (56.8)
Chronic sleep disturbances, no diabetes	303 (23.5)	157 (21.9)	325 (26.8)	236 (22.9)
Diabetes, no chronic sleep disturbances	198 (15.4)	142 (19.8)	160 (13.2)	136 (13.2)
Diabetes and chronic sleep disturbances	127 (9.9)	52 (7.2)	136 (11.2)	73 (7.1)
Nutritional values				
Total Calories per day (mean, SD)* +	1716 (703)	2436 (1013)	1422 (582)	2258 (874)
Alternate Mediterranean diet score (mean, SD)* +	2.2 (0.9)	6.7 (0.8)	1.5 (0.7)	6.7 (0.8)

*p<0.001 men, +p<0.001 women; **p<0.05 men, ++p<0.05 women

Table 4.3 Odds ratio of consuming a healthy diet due to comorbidity of diabetes and chronic sleep disturbances, by gender.

Men	Adjusted for age and caloric intake	Adjusted for additional covariates*
No diabetes, no sleep disturbances	REF	REF
Sleep disturbances, no diabetes	0.86 (0.67-1.11)	1.02 (0.78-1.34)
Diabetes, no sleep disturbances	**1.45 (1.11-1.91)**	**1.70 (1.25-2.29)**
Both diabetes and sleep disturbances	0.73 (0.50-1.07)	1.03 (0.67-1.56)

Women	Adjusted for age and caloric intake	Adjusted for additional covariates*
No diabetes, no sleep disturbances	REF	REF
Sleep disturbances, no diabetes	**0.71 (0.56-0.90)**	0.87 (0.67-1.12)
Diabetes, no sleep disturbances	0.83 (0.62-1.12)	1.15 (0.82-1.62)
Both diabetes and sleep disturbances	**0.53 (0.37-0.77)**	0.81 (0.54-1.22)

Data are OR (95% CI). Odds of being in the highest quartile of the gender-specific Mediterranean Diet score vs the lowest quartile.
REF: Reference group in all models are those without chronic sleep disturbances or diabetes.
*Multivariate models are adjusted for age, daily caloric intake, race/ethnicity, education, employment status, marital status, hypertension, depression, smoking, physical activity and obesity

Table 4.4 Multivariate linear regression assessing the association between diabetes and chronic sleep disturbances and the aMedDiet score.

Full Study Population	**Estimate (95% CI)**	**p**
No diabetes, no sleep disturbances	REF	
Sleep disturbances, no diabetes	0.03 (-0.13-0.20)	0.70
Diabetes, no sleep disturbances	**0.22 (0.06-0.37)**	0.01
Both diabetes and sleep disturbances	**-0.14 (-0.25- -0.03**)	0.02

REF: Reference group in all models are those without chronic sleep disturbances or diabetes.
*Multivariate models are adjusted for age, gender, daily caloric intake, race/ethnicity, education, employment status, marital status, l
depression, smoking, physical activity and obesity

Supplemental Tables

Table 4.S1 Baseline characteristics of the study population.

	Men	Women	All
	n= 2994	n= 4429	n=7423
Demographic Characteristics	# (%)	# (%)	# (%)
Age (mean yrs, SD)	65.2 (10.5)	64.9 (11.4)	65.0 (11.0)
Race/Ethnicity*			
White/other, non-Hisp	2225 (74.3)	3145 (71.0)	5370 (72.3)
Black, non-Hisp	405 (13.5)	777 (17.5)	1182 (15.9)
Hispanic	364 (12.2)	507 (11.4)	871 (11.7)
Education*	13.5 (3.0)	12.9 (2.8)	13.1 (2.9)
<High school	618 (20.6)	892 (20.1)	1510 (20.3)
High school	1364 (45.6)	2260 (51.0)	3624 (48.8)
Some college	172 (5.7)	314 (7.1)	486 (6.5)
College/Professional degree	840 (28.1)	963 (21.7)	1803 (24.3)
Currently married*	2254 (75.3)	2469 (55.7)	4723 (63.6)
Currently working*	1262 (42.2)	1675 (37.8)	2937 (39.6)
Health Behaviors			
Weekly moderate or vigorous phys activity*	2174 (72.6)	2803 (63.3)	4977 (67.0)
Current smoker**	443 (14.8)	571 (12.9)	1014 (13.7)
Alcohol use >= 2d/wk*	1000 (33.4)	914 (20.6)	1914 (25.8)
Health Conditions			
Diabetes**	799 (26.7)	1069 (24.1)	1868 (25.2)
Hypertension	1714 (57.2)	2479 (56.0)	4193 (56.5)
Heart disease*	741 (24.7)	804 (18.2)	1545 (20.8)
Heart attack*	280 (9.4)	182 (4.1)	462 (6.2)
Depression*	358 (12.0)	993 (22.4)	1351 (18.2)
BMI (mean, SD)*	917 (46.7)	1349 (48.2)	2266 (47.6)
Normal weight	369 (12.3)	928 (21.0)	1297 (17.5)
Overweight	1211 (40.4)	1363 (30.8)	2574 (34.7)
Obese	1414 (47.2)	2138 (48.3)	3552 (47.9)
Chronic sleep disturbances			
Trouble falling asleep, most of the time*	293 (9.8)	712 (16.1)	1005 (13.5)
Trouble waking up at night, most of the time*	709 (23.7)	1102 (24.9)	1811 (24.4)
Trouble waking up too early*	358 (12.0)	601 (13.6)	959 (12.9)
One or more chronic sleep disturbance*	937 (31.3)	1559 (35.2)	2496 (33.6)
Comorbidity of diabetes and chronic sleep disturbances*			
No diabetes diagnosis/no chronic sleep disturbance	1527 (51.0)	2253 (50.9)	3780 (50.9)
Chronic sleep disturbances, no diabetes	668 (22.3)	1107 (25.0)	1775 (23.9)
Diabetes, no chronic sleep disturbances	530 (17.7)	617 (13.9)	1147 (15.5)
Diabetes and chronic sleep disturbances	269 (9.0)	452 (10.2)	721 (9.7)
Nutritional values			
Total Calories per day (mean, SD)*	2013 (890)	1797 (812)	1884 (851)
Alternate Mediterranean diet score (0-9) (mean, SD)	4.0 (2.0)	3.9 (2.0)	4.0 (2.1)

*p<0.001,**p<0.05

Table 4.S2 The Alternate Mediterranean diet scoring system in the Health and Retirement Study.

	Criteria for Maximum Score (1)		
Component	**Men**	**Women**	Full Sample
Fruit (**a**), servings/day	>1.7	>1.8	>1.6
Vegetables (**b**), servings/day	>2.3	>2.5	>2.3
Whole grains (**c**), servings/day	>0.6	>0.6	>0.6
Red/processed meats (**d**), servings/day	<0.7	<0.5	>0.6
Alcohol (**e**), servings/day	>.5, <=2	>.5, <=1.5	>.5, <=2
Nuts (**f**), servings/day	>0.4	>0.3	>0.4
Legumes (**g**), servings/day	>0.1	>.1	>0.1
Fish (**h**), servings/day	>.2	>.2	>0.1
MUFA/SFA	>1.1	>1.0	>0.2

Abbreviations: MUFA: monounsaturated fats; SFA: saturated fats.
The cut-offs were based on the median intake values by gender, as well as for the full sample, from the original population, with the exception of alcohol. For alcohol, 1 point was given for moderate intake, 0 points were given for no alcohol or heavy alcohol consumption. For red/processed meats, 1 point was given for consumption below the median. Apart from alcohol and red/processed meats, 1 point is given for values above the gender-specific median value.

aIncludes whole fruit and fruit juice. One serving is 1 medium piece of fruit or 0.5 cup of berries or a small glass of fruit juice.
bIncludes all vegetables except potatoes. One serving is 0.5 cup of vegetables or 1 cup of green leafy vegetables.
cOne serving is 1 cup of cooked oatmeal, brown rice or other grain (bulghur, kasha, buckwheat) or 1 slide of dark or wheat bread.

dOne serving is 4 oz of unprocessed meat or 1.5 oz of processed meat.

eOne serving is one bottle of beer, a 5 oz glass of wine, or 1 drink or shot of liquor

fOne serving is 1 oz of nuts or 1 tablespoon of peanut butter

gOne serving is 0.5 cup

hOne serving is 2-5oz.

Chapter 5 Discussion

Summary & implications of main findings

Our research provides new evidence on the multi-directional association between chronic sleep conditions and chronic diseases. We live in an aging society. It is estimated that between 2012 and 2035 the percentage of the U.S. population aged 65 and older will increase from 14% to 22% representing an increase of over 20 million individuals in this age range (1). Given the increased health care costs among older adults, an emphasis should be placed on healthy aging. Over 60% of adults aged 65 and older have at least one chronic condition. Twenty-five percent have 3 or more chronic conditions (2). Comorbidity of chronic conditions leads to extensive health care costs at the individual as well as societal levels. Our research has provided further support that chronic sleep disturbances are associated with new chronic conditions, type II diabetes specifically, and may also be considered a comorbid health condition among those with existing diabetes as it leads to impaired glucose tolerance and insulin sensitivity (shown previously) and leads to disturbances in healthy eating which is critical for those with diabetes.

Several over-arching novelties exist in this research including:

- The focus on sleep quality rather than sleep duration as it relates to chronic conditions. Sleep quality may be easier for individuals to assess compared to sleep duration as it is a subjective measure, to some degree. When relying on self-reported measures, sleep duration is often mis-reported as we do not know exactly what time we fall asleep nor the exact duration of time spent awake at night. Previous studies have demonstrated a U-shaped relationship between sleep

duration and mortality, cancer and cardiovascular disease. Those who sleep less than six hours a night or more than ten hours are at increased risk of mortality and development of chronic diseases compared to those who sleep seven to eight hours a night. Although results have varied, previous studies have found that men with increased sleep duration appear to have the greatest risk of mortality and developing chronic conditions. Women tend to report higher levels of short and long-term sleep disturbances. However, fewer studies have assessed the association between sleep disturbances, or poor sleep quality, and the development and progression of disease. Sleep duration does not inform us of sleep quality, or where in the sleep cycle disturbances may have occurred. Disruptions in sleep quality may be better predictors of disease risk than sleep duration as sleep duration can be misclassified as "normal" duration if, for example, individuals with poor quality sleep due to sleep disruptions tend to stay in bed longer to attempt to make up the lost sleep. Additionally, some precision may be lost when asking participants in population-based studies to report sleep duration. This lack of precision could lead to measurement error in the form of over or under-reporting sleep duration. Sleep quality may be easier to assess. Self-reported sleep quality is assessed with questions on difficulty falling asleep and difficulty staying asleep. These qualitative measures may be easier to report accurately than the quantitative measure of duration. Studies utilizing actigraphy or wearable fitness monitors have found a good correlation between self-reported measures of sleep quality and sleep disturbances measured via actigraphy.

- The analyses were stratified by gender, thereby allowing for the assessment of variation in the associations between other covariates of interest and known confounders, which may vary by gender as well as the relationship between chronic sleep disturbances and type II diabetes. The large sample size of the Health and Retirement Study allowed for stratification by gender to

assess these associations, several of which had not been reported previously. Additionally, we were able to quantify the difference in risk for women versus men for the various associations between chronic sleep disturbances and diabetes. This research highlights the importance of sleep quality, especially among women. Poor quality or inadequate sleep can be considered a life course issue as it affects individuals at various points over the course of life (newborns, teenagers, young adults, during menopause, older adults). It may be that the cumulative burden of poor quality sleep over the life course is greater for women. While other studies will be able to address sleep disturbances at critical times, we are able to show that the multi-directional association between chronic sleep disturbances and diabetes is greater in women than men in each of our three papers.

- Also due to the large sample size, as well as the oversample of Black and Hispanic minority populations in the Health and Retirement Study, our research is able to provide new and additional information regarding chronic sleep disturbances and the association with a chronic condition among a multi-ethnic population of older adults. While previous studies have assessed differences in sleep quality by race and ethnicity, longitudinal studies of these associations and how they vary by race/ethnicity within gender have not been reported.

- The assessment of chronic conditions as potential confounders and/or mediators in the relationship between chronic sleep disturbances and type II diabetes in our research has shown that individuals with comorbidity of multiple chronic conditions are more likely to develop chronic sleep disturbances. When we consider chronic sleep disturbances as a comorbid condition in the presence of type II diabetes, we observe an antagonist effect between the conditions which leads to poor dietary intake.

Novel Findings

Aim 1: Previous longitudinal studies assessing the association between chronic sleep disturbances and incident diabetes focused primarily on sleep duration, rather than sleep quality (3, 4). Most of these studies were unable to report differences by gender. Data reported from the United States on the association between chronic sleep disturbances and incident diabetes has primarily been cross-sectional in nature (5-7). To our knowledge, this is the first population-based study from the U.S. to report a longitudinal association between chronic sleep disturbances and incident diabetes as well as to provide information by gender and race/ethnicity. As our society shifts to individualized medicine, a better understanding of individual level risk factors is important in the prevention, detection and treatment of disease. In our study, we found that women suffer from chronic sleep disturbances at a higher rate than men and have a greater likelihood of developing type II diabetes in the presence of chronic sleep disturbances.

Aim 2: While previous studies have assessed chronic sleep disturbances as an antecedent of type II diabetes as well as the prevalence of chronic sleep disturbances among those with diabetes, population-based studies have not assessed the development of new chronic sleep disturbances after diagnosis of type II diabetes. Given the negative effects of chronic sleep disturbances on glycemic regulation and inflammation, the new development of chronic sleep disturbances may play an important role in the development and progression of chronic conditions as a result of uncontrolled diabetes (Trento 2008, 4). Our study detected an increased association of developing new chronic sleep disturbances within four years of diagnosis of diabetes in women, but not in than men.

Aim 3: Our study found an antagonistic association of chronic sleep disturbances among those with type II diabetes leading to lower intake of a healthy diet. To our knowledge, this is the

first study to assess the joint associations of chronic sleep disturbances and chronic conditions on dietary intake. One of the first areas of intervention among those newly diagnosed with diabetes is regarding dietary intake as the composition of one's diet is key in maintaining glycemic control among those with type II diabetes (American Diabetes Association, 2016). The Mediterranean diet has previously been found to be both protective against the development of type II diabetes as well as a healthy diet among those with type II diabetes. We found that men with type II diabetes are more likely to consume a healthier diet, such as a Mediterranean-style diet, unless they are also experiencing chronic sleep disturbances. However, it does not appear that older adult women with type II diabetes consume a healthy diet and the odds of doing so are even lower in the presence of chronic sleep conditions.

Gender and Chronic Sleep Disturbances

In each of the three primary aims, differences in associations were detected for men and women. Women appear to suffer from chronic sleep disturbances to a greater degree than men and the association between chronic sleep disturbances and incident diabetes appears to be greater in women than men. Additionally, chronic sleep disturbances among women with diabetes appears to have a negative association with healthy dietary intake. There are several potential reasons for the gender-based differences detected in our research. First, it is possible that men underreport chronic sleep disturbances when self-reported measures are used. Next, as women age and experience hormonal changes related to menopause, an increase in chronic sleep disturbances may occur. While the majority of our study population had likely completed their menopausal transition at the time of participation, unresolved disruptions in circadian rhythms or sleep disturbances may have still existed. Women report higher rates of other chronic conditions, such as pain, incontinence and depression and anxiety which are also associated with sleep

disturbances. Medications taken for these same conditions may also lead to increased nocturnal as well as sleep disruptions. Additionally, women may be more susceptible to other environmental factors or psychosocial stressors that are associated with chronic sleep disturbances. Future research in the field of genetics will help us better understand the potential genetic differences in chronic sleep disturbances among men and women, as well as the proportion of disturbances attributable to genetics versus other environmental or emotional and physical health factors.

Strengths

This research has several strengths. The data utilized to assess these three areas of research are representative of the U.S. population over the age of 50 thus allowing for the generalizability of the results to the broader U.S. population. Additionally, the high response rates achieved by the Health and Retirement Study as well as the panel retention rates decrease the potential for non-response bias due to loss to follow-up. The bi-annual response rates often approach 90% and the response rate for the Health Care and Nutrition Mail Survey, utilized in aim 3, was close to 70%. The large sample size and inclusion of a minority oversample allows for the detection of associations by gender and race/ethnicity. Additionally, the analysis of blood spot samples among a random half of the study population every two years allowed for the detection of approximately thirty-percent more cases of diabetes than by self-report alone. It is estimated that 25% of those with type 2 diabetes in the U.S. are not diagnosed.

Limitations

The primary limitation of this research is the reliance on self-reported measures of type II diabetes and chronic sleep disturbances. Self-reported measures are subject to measurement errors such as recall bias, over- or under-reporting, potentially due to social desirability. It is

possible that self-reported sleep disturbances among men were under-reported, as other studies have found (American Community Survey). The inability to clinically validate either of these measures, type II diabetes and chronic sleep disturbances, is a limitation. However, the incidence and prevalence rates of both type II diabetes and chronic sleep disturbances are similar to those previously reported which is reassuring. The frequency of the measurements is a limitation as well. Chronic sleep disturbances were assessed every four years and incident diabetes is assessed every two years. Thus, the precision of the dates in which these conditions first appeared is unknown and changes in conditions between interview dates is not known either. Finally, we cannot determine the impact of unmeasured confounders in the associations we have detected. At this time, information on family history of disease or the presence of other health conditions related to chronic sleep disturbances, such as sleep apnea and restless leg syndrome, is not available for our study population.

Towards public health and policy

Sleep is a basic biological need (3). Sleep is also a modifiable risk factor. While many interventions target increased physical activity and a healthy diet, few have targeted healthy sleep conditions. However, several public health campaigns have focused on sleep conditions among subgroups of populations. This has included the “Back to Sleep” campaign to reduce the risk of sudden infant death syndrome (SIDS) in newborns as well as recent legislation to shift the start time of high school classes given new knowledge of the circadian rhythms of adolescents and the decreased sleep that potentially leads to negative mental and physical health consequences. Professional associations, such as those regulating airplane pilots or truck drivers, have also begun to provide restrictions on shift durations given the increased rates of accidents and other health-related risks due to prolonged lack of sleep. While the National Sleep

Foundation has recently promoted a “national sleep awareness week”, additional focus should be placed on providing information to the public regarding the need for quality sleep. Previously, the focus has primarily been on sleep duration. However, sleep duration varies by age and by individual. Some individuals function well with six hours of sleep on a regular basis while others need a full eight hours. Additionally, it is not only sleep duration, but also sleep quality that increases the risk for the development and progression of other chronic conditions, as we have shown. Our study and others have shown that waking up at night and being unable to fall back asleep is the most frequent sleep disruption and may also be the most harmful in terms of increasing risk for other chronic conditions. Our current society seems to reinforce disrupted sleep given the ability, and expectation in some circumstances, to be connected and engaged around the clock. Public awareness of the deleterious effects of disrupted sleep must be increased. Additionally, greater awareness of sleep hygiene techniques that are useful to help one return to sleep must be increased. While prevention is necessary, early detection of chronic sleep disturbances is key as well. Physicians and clinicians must begin to incorporate an assessment of sleep disturbances into their clinical practice in order to detect early stages of chronic sleep disturbances, which is when interventions are most successful. The rapid increase in the use of over-the-counter sleep aides is indicative of the increased rate of sleep disturbances and, potentially, the lack of discussion of other useful techniques in improving sleeping conditions and sleep quality.

Future directions

Further studies of disruptions of sleep over the life course and the impact on longer term development and progression of chronic conditions is necessary. While we have provided additional, and new, evidence of the deleterious and multi-directional effects of poor sleep

quality and type II diabetes, the association with other chronic conditions related to inflammation should be assessed as well. Additionally, we must continue to explore these relationships taking into account the potential for variation due to gender and race/ethnicity, some of which is due to society and environmental conditions as well as potential genetic differences. The field of genetic research is expanding our knowledge of the predisposition for certain health conditions. Recent studies have detected genetic predisposition for chronic sleep disturbances which will improve our ability to provide individualized recommendations in the prevention and treatment of sleep disturbances. Additionally, the development of sensors and wearables, such as Fitbits, allow for both increased individual awareness of one's sleep patterns as well as provide a new means of objectively measuring both sleep duration and sleep quality. As these devices become more prominent, both in the U.S. and internationally, costs will decrease and data sharing will become more prevalent, thus facilitating use in population-based research.

Conclusion

The focus on the effects of sleep disturbances on health, in terms of the epidemiology and physiology, is recent. As an example, a PubMed search on the terms "diabetes" and "sleep quality", "sleep disruptions" or "sleep disturbances" yielded 2 citations between 1980-1989, 13 citations between 1990-1999, 90 citations between 2000-2009, and 453 citations between 2010-2017 with close to 60% of those published in the last two years (between 2015-2017) (www.ncbi.nlm.nih.gov/pubmed, doi 11-25-2017). The first textbook on sleep epidemiology, *Sleep, health and society: from aeitology to public health*, was published in 2010. In the foreward, Professor Sir Michael Marmot ponders "Is sleep a cause, a symptom or a consequence?" Lead editor Francesco Cappuccio reiterates this question as it relates to various

health conditions throughout the book. This dissertation attempts to help address this question, as it relates to diabetes.

References

1. An aging nation: the older population in the U.S. Centers for Disease Control, 2014. https://www.census.gov/prod/2014pubs/p25-1140.pdf

2. Chronic disease overview. Centers for Disease Control, 2012. https://www.cdc.gov/chronicdisease/overview/index.htm

3. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33:414-420.

4. Knutson KL, Ryden AM, Mander BA, VanCauter E. Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. Archives of Internal Medicine. 2006. 166:1768-1774.

5. Zizi F, Pandey A, Murrray-Bachmann R, Vincent M, McFarlane S, Ogedegbe G, Girardin JL, Race/ethnicity, sleep duration, and diabetes mellitus: analysis of the National Health Interview Survey. The American Journal of Medicine. 2012;125: 2. 162-167.

6. Ayas N, White D, Al-Delaimy W, Manson J, Stampfer M, Speizer F, Patel S, Hu F. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care. 2003. 26:2,380-384.

7. Gangwish J, Heymsfield S, Boden-Albala B, Bujis R, Kreier F, Pickering T, Rundle A, Zammit G, Malaspina D. Sleep duration as a risk factor for diabetes incidence in a large US sample. Sleep. 2007. 20:12,1667-1673.

8. Trento M, Broglio F, Riganti F et al. Sleep abnormalities in type 2 diabetes may be associated with glycemic control. Acta Diabetologia. 2008. 45:225-229.

9. Ohayon M, Wickwire EM, Hirshkowitz M, Albert SM, Avidan A, Daly FJ, et al. National Sleep Foundation's sleep quality recommendations: first report. Sleep Health. 2017.(3):6-19.

10. Perry GS, Pail SP, Presley-Cantrell LR. Raising awareness of sleep as a healthy behavior. Prev Chron Dis. 2013. 10:130081. DOI: http://dx.doi.org/10.5888/pcd10.13008.

11. Scott SK, Harris RE. Epidemiology of diabetes mellitus. In Epidemiology of Chronic Disease: Global Perspectives. Jones & Bartlett Learning, LLC, 2013. p.3 75-416.

12. Cappuccio F, Miller M, Lockley S. Sleep, Health, and Society: From Aetiology to Public Health. 2010. New York. Oxford University Press.