EXAMINING THE ROLE OF SLEEP DURATION ON THE RISK OF HYPERTENSION, STROKE, AND MORTALITY

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAI'I AT MĀNOA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

EPIDEMIOLOGY

DECEMBER 2021

By

Yosuke Kawai

Dissertation Committee:

Andrew Grandinetti (chairperson)
Gertraud Maskarinec
Yurii Shvetsov
Eric Hurwitz
Carol Boushey

ACKNOWLEDGMENTS

Firstly, thank you very much to all the MEC participants, investigators, and staff who made this research possible.

Next, I would like to express my gratitude to my committee members for their guidance and support during this PhD journey. Dr. Maskarinec, thank you very much for involving me in your research a few years ago. Without you, I may have never been involved with the UH Cancer Center and may have never considered sleep research as a research topic. Dr. Shvetsov, thank you very much for always responding to my statistic and coding questions and being patient with me as I struggled to understand difficult concepts. Dr. Boushey, thank you very much for your willingness to join the team even though you had an extremely busy schedule. Dr. Hurwitz, thank you very much for your lessons on epidemiological concepts and methods in the last few years. Dr. Grandinetti, thank you very much for your willingness to be my committee chair and guiding me through my writing and analysis. You have always pushed me to do better, and I hope I made you proud.

I also want to give my biggest mahalo to my ‘ohana at the Office of Public Health Studies and the CTO at the UH Cancer Center. Thank you very much for supporting my studies through graduate assistantships and scholarships. I want to give a special shout out to Cherie, Fadi, and Maryssa for being such an awesome colleague, friend, and rival. Thank you very much for your helping hand and guidance whenever I got lost (which occurred quite often).

I would like to express my sincerest gratitude and appreciation to my mom, dad, and my two brothers. You all gave me the freedom and encouragement to pursue this degree, and I hope I made you proud. I wanted to also say thank you very much to all my friends who has encouraged me and supported me during rough times. To Jon, Kellen, and Kristen, thank you

very much for helping me stay sane with weekly tennis and socializing. Finally, thank you very much to Han Ha, my longtime partner. Thank you very much for always willing to listen to my gripes and doing everything you can to help me in stressful situations.

ABSTRACT

Sleep duration and quality have been recently gaining interest as modifiable risk factors for morbidity and mortality. Many epidemiological studies suggest that sleep duration, both short and long hours, is an important risk factor for type 2 diabetes, obesity, cancer, cardiovascular disease, hypertension, stroke, and mortality. While the exact mechanism linking sleep and disease is unclear, it is believed to involve complex interactions between metabolic, endocrine, and immune pathways.

The three studies presented in this dissertation examined the association between sleep duration and hypertension, stroke, and mortality and informed the hypotheses that sleep durations deviating from the recommended 7 to 8 hours would be associated with increased risk for these outcomes. In each of these studies, the potential for demographic characteristics and medical conditions to modify the relationship between sleep duration and the main study outcomes were investigated. All three study aims in this dissertation used data from the Multiethnic Cohort (MEC) study, a large, ethnically diverse prospective cohort study of middle-aged and elderly adults in Hawai'i and Los Angeles.

In the first study, sleep duration was found to be weakly associated with prevalent hypertension, but not incident hypertension. There was also no evidence of effect modification by age, sex, ethnicity, or BMI. In the second study, sleep duration was associated with a 13% and 39% increased risk of incident stroke in those who reported ≤5 and ≥10 hours of sleep, respectively. There were no significant differences across age, sex, ethnicity, BMI, hypertension status, or diabetes status. In the third study, sleep duration was associated with an increased risk of all-cause, cardiovascular, and stroke mortality. Those reporting ≥10 hours of sleep were at a 43%, 48%, 66% increased risk of all-cause, cardiovascular, and stroke mortality, respectively.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ADA	American Diabetes Association
AHA	American Heart Association
ANOVA	Analysis of variance
ARIC	Atherosclerosis Risk in Communities
AVAIL	Adherence Evaluation After Ischemic Stroke – Longitudinal
BMI	Body mass index
BRFSS	Behavioral Risk Factor Surveillance System
CARDIA	Coronary Artery Risk Development in Young Adults
CALIBER	Cardiovascular Research Using Linked Bespoke Studies and Electronic Health Records
CDC	Centers for Disease Control and Prevention
χ^2	Chi-square test
CI	Confidence interval
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
Diabetes	Diabetes mellitus (Type 2)
DQS	Dietary Quality Score
EPIC	European Prospective Investigation into Cancer and Nutrition
g	Grams
GABA	Gamma-aminobutyric acid
GBD	Global Burden of Disease
GCNKSS	Greater Cincinnati/Northern Kentucky Stroke Study
HTN	Hypertension
HR	Hazard ratio
ICD	International Classification of Disease
INTERMAP	International Study of Macro/Micronutrients and Blood Pressure
JPHC	Japan Public Health Center
kg	Kilogram
L.A.	Los Angeles
m	Meters
MEC	Multiethnic Cohort
MET	Metabolic equivalent of task
mg	Milligrams
mm Hg	Millimeters of mercury
MVPA	Moderate-to-vigorous physical activity
n	Number (of participants)
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIH	National Institutes of Health
NOMAS	Northern Manhattan Study
OR	Odds ratio
OSA	Obstructive sleep apnea

PR	Prevalence ratio
PSQI	Pittsburgh Sleep Quality Index
Qx	MEC questionnaire
RCT	Randomized controlled trial
RD	Risk difference
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	Risk ratio
SBP	Systolic blood pressure
SD	Standard deviation
SHHS	Sleep Heart Health Study
U.S.	United States
WHR	Waist-to-hip ratio

CHAPTER 1: INTRODUCTION

1.1 Epidemiology of Sleep

Sleep behaviors and patterns, such as its quantity and quality, are recently gaining interest as modifiable risk factors for mortality and morbidity. In the past 50 years, sleep patterns have changed drastically around the world, characterized mainly by the increasing prevalence of sleep deprivation [1]. With the exception of one study [2], recent large-scale studies conducted in the U.S. also indicated a decreasing trend of sleep duration [3-6]. Based on these studies, the mean sleep duration in the U.S. today appears to be approximately 7 hours per night and about one-third of the population is sleeping less than 7 hours (Table 1). According to the 2014 BRFSS and NHIS data, sleep duration was also found to differ by age, sex, and ethnicity (Table 2). Some factors associated with a higher prevalence of short sleep were being female, being of ages 35-54 years, and being African American, American Indian, or multiracial [4, 6].

The increasing prevalence of sleep deprivation is likely caused by a variety of factors, such as increases in environmental light [7], longer workdays and commuting time [7, 8], an increase in shift work and night work [9], and personal technology use [10, 11].

Table 1. Summary of recent studies discussing the prevalence of short sleep in the U.S.

Publication Year	**Data Source (Year)**	**Summary**
2015 [3]	• NHIS • 1985, 1990, 2004-2012	• Age-adjusted mean sleep duration were 7.4 hours (1985), 7.29 hours (1990), and 7.18 hours (2004). • Age-adjusted prevalence of short sleep (≤6 hours) was 22.3% in 1985 and 29.2% in 2012. • 70.1 million US adults reported short sleep in 2012.
2018 [2]	• American Time Use Survey (Bureau of Labor Statistics) • 2003-2016	• Weekday and weekend sleep duration increased by 1.4 and 0.83 min/year, respectively. • Decreased sleep duration seen in those aged 35–74 years • Prevalence of short (≤7), normal (>7-9), and long sleep (>9) changed by -0.44%, -0.03%, and 0.48%/year, respectively.
2020 [4]	• BRFSS • 2014	• Age-adjusted prevalence of short sleep (<7 hours) was 35.2%. • Sleep duration varied by age, sex, ethnicity, and geographic location

2020 [5][a]	• Sleep Cycle Study (New York)
	• 2015-2018
		• Mean sleep duration = 7.11 hours
		  ○ Women: 7.27 hours
		  ○ Men: 7 hours
		• Longer sleep duration on older participants compared to younger.

2020 [6]	• NHIS • 2010-2018	• Prevalence of short sleep (≤6 hours) was 30.9% in 2010 and 35.6% in 2018. • Odds of short sleep duration 25% higher in 2018 compared to 2010 (adjusted for demographic and occupational characteristics). • Significant variation by age, sex, race, education, marital status.

[a]utilized a sleep tracker application

Table 2. Comparison of age-adjusted prevalence of short sleep duration (<7 hours) between the 2014 BRFSS and NHIS data by age, sex, and ethnicity [4, 6].

	Prevalence (%)	
Characteristic	**BRFSS**	**NHIS**
All adults	35.2	33.0
Sex		
Men	35.5	32.7
Women	34.8	33.3
Age groups		
18-24	32.2	27.6
25-34[a]	37.9	32.7
35-44[a]	38.3	N/A
45-54[b]	39	35.6
55-64[b]	35.6	N/A
≥65	26.3	28.5
Race/ethnicity		
White	33.4	31.0
Hispanic	34.5	33.9
African American	45.8	44.8
Asian	37.5	32.4
American Indian/Alaskan Native	40.4	45.2
Native Hawaiian/Pacific Islander	46.3	N/A
Other/Multiracial	44.3	39.9

[a]the NHIS combined these age categories to 25-44.
[b]the NHIS combined these age categories to 45-64.

1.2 Sleep Duration as a Risk Factor

In the past 30 years, the increasing prevalence of sleep deprivation has been gaining attention as a major public health concern, partly due to discoveries linking poor sleep to the incidence of various diseases [12]. Even more recently, excess sleep has become a topic of interest for its potential role in various disease etiology. To date, many epidemiological studies suggest that sleep duration, both short and long, is an important risk factor for diabetes [13-19], obesity [16, 19-24], cancer [25-27], cardiovascular disease [20, 28-30], hypertension [31-33], stroke [19, 34-36], cognitive impairment [37-39], and early mortality [19, 29, 40-42]. The physiological link between sleep and these outcomes is unclear and complex, but is believed to involve various metabolic, endocrine, and immune pathways [16, 20].

There are numerous epidemiological evidence suggesting a strong link between sleep duration and type 2 diabetes risk [14, 17-19]. In the Sleep Heart Health Study (SHHS), sleep duration was measured using both subjective and objective methods, and the odds of diabetes was elevated by 151% and 66% among participants sleeping ≤5 and 6 hours, respectively [14]. The odds of diabetes were also elevated among participants reporting ≥9 hours of sleep (OR: 1.79). This elevation in diabetes risk in both extremes of sleep has also been reported in some meta-analysis reports [17, 18]. However, the magnitude of association differed by study, and there is also a report that only found an association among long sleepers [13].

Obesity is one of the most studied diseases in relation to sleep, with associations reported across all age groups. In a review of studies involving children, short sleep was found to increase the odds that the child will be overweight or obese by 71% [22]. In a more recent meta-analysis of 42 prospective studies involving children, short sleep was associated with a 40%, 57%, and 30% increased risk of obesity among children in infancy, early childhood, and adolescence,

respectively [23]. This strong association between short sleep and obesity is also reported in adults. In one meta-analysis of 16 independent cohort samples, short sleep was associated with a 38% increased risk of obesity [19]. In contrast, long sleep appeared to be either weakly or not associated with obesity risk [21, 24].

In sleep literature, there seems to be a consensus that obstructive sleep apnea (OSA) and clinically diagnosed insomnia are strong risk factors for cancer [43-45]. However, research findings on the role of sleep duration specifically have been inconsistent. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, short sleep (<6 hours) was associated with a 43% increase in the risk of cancer [34]. In comparison, a recent meta-analysis only found an 8% increase in cancer risk among participants reporting 4-5 hours of sleep per night [27]. In addition, 6 hours of sleep was not found to be associated with cancer risk. The study also reported only a 5% increase in the risk of cancer among long sleepers. While these studies reported associations among short sleepers, there are also studies that found no association [25] or only found associations in certain types of cancer [26]. Based on these reports, it is difficult to determine if sleep duration is truly associated with cancer risk.

The association between sleep duration and hypertension has been gaining a lot of interest because of the burden of hypertension globally. In the Sleep Heart Health Study (SHHS), compared to middle-aged and elderly adults reporting 7 to <8 hours of sleep, those reporting <6 hours of sleep and >9 hours of sleep were at 66% and 30% increased odds of hypertension, respectively [31]. As an example of a study that used an objective sleep measure, the Coronary Artery Risk Development in Young Adults (CARDIA) study used actigraphy and found a 37% increase in odds of incident hypertension for each 1-hour reduction of sleep [33].

There is already an established link between sleep and stroke, evidenced by treatments of common sleep disorders as part of post-stroke regimens [46]. The role of sleep duration is relatively understudied, but there is evidence that both sleep deprivation and excess sleep may be an independent risk factor for stroke. In the Takayama Cohort Study, long sleep duration (≥9 hours) was associated with a 51% increase in total stroke mortality [30]. In the European Prospective Investigation into Cancer (EPIC) study in Potsdam, both short and long sleep were found to increase the risk of incident stroke by 106% and 65%, respectively [34].

Sleep duration was also shown to be a risk factor for early mortality. In the Multiethnic Cohort (MEC) study, compared to participants reporting 7 hours of sleep, participants reporting ≤5, 8, and ≥9 hours were at a 15%, 7%, and 19% increased risk of all-cause mortality [29].

1.3 Research Questions of this Dissertation

This dissertation focused on the association between sleep duration and: 1) hypertension, 2) stroke, and 3) mortality. In addition, this dissertation also aimed to uncover the role of various demographic and medical history characteristics that could potentially modify these relationships.

1.3.1 Research Question 1: Sleep and Hypertension

The first aim of this dissertation was to investigate the association between sleep duration and hypertension using both a cross-sectional and longitudinal study design. The association between sleep duration and prevalent hypertension was assessed using data from the baseline questionnaire (1993-1996). Incident hypertension was studied by also incorporating data from three follow-up questionnaires (Qx2, 3, and 4). The hypothesis of this study was that both short sleep and long sleep hours, compared to the recommended 7 hours, contributes to increased hypertension risk. It was hypothesized that this association would differ by age, sex, ethnicity,

and BMI. Based on a literature review, it was expected for the association to be stronger in younger participants (vs. older), males (vs. females), African American and Native Hawaiian participants (vs. Whites), and obese participants (vs. healthy weight BMI).

1.3.2 Research Question 2: Sleep and Stroke

The second aim of this dissertation was to investigate the association between sleep duration and incident stroke. The risk of stroke was evaluated based on the first stroke episode, using information from all four questionnaires. The hypothesis of this study was that there would be a J-shaped association between sleep duration and incident stroke. This association was expected to differ by age, sex, ethnicity, BMI groups, with the nature of the association hypothesized to be similar to what was discussed in section 1.3.1. In addition, it was also expected for the association to differ based on the participants' hypertension and diabetes status at baseline, where the association between sleep and stroke would be stronger in participants with these comorbidities.

1.3.3 Research Question 3: Sleep and Mortality

The third aim of this dissertation was to investigate the association between sleep duration and all-cause, cardiovascular, and stroke mortality. The hypothesis of this study was that there would be a U- or J-shaped association between sleep duration and mortality. This association was expected to differ by age, sex, ethnicity, BMI groups, with the nature of the association hypothesized to be similar to what was discussed in section 1.3.1.

1.4 Data Source: The Multiethnic Cohort (MEC)

To study these three research questions, this dissertation used data from the Multiethnic Cohort (MEC) study. The MEC is a large, population-based prospective study consisting of more than 215,000 residents in Hawai'i and Los Angeles. The participants were men and women, aged 45 to 75 years, from five main ethnic groups: White, African American, Native Hawaiian, Japanese American, and Latino. The main objective of the MEC was to examine lifestyle and genetic risk factors responsible for disparities in cancer incidence and mortality across the five ethnic groups. Participants were identified by ethnic-specific surnames and first names in driver's license records in Hawai'i and Los Angeles [47]. The initial survey, conducted in 1993–1996, was a self-administered 26-page questionnaire that inquired about various demographic, anthropometric, dietary, and lifestyle factors, as well as medical history. Dietary information was obtained using a validated food frequency questionnaire that included foods commonly consumed by the five main ethnic groups in the study [48]. After the initial survey (called Questionnaire 1, or Qx1), follow-up questionnaires were sent to the participants at approximately 5-year intervals. In this dissertation, questionnaire responses from Qx1, Qx2 (1998–2002), Qx3 (2003–2008), and Qx4 (2008–2012) will be analyzed. As described in Chapter 4, the MEC was linked to Vital Records in Hawai'i and Los Angeles to identify deaths among the cohort members.

CHAPTER 2: ASSOCIATION BETWEEN SLEEP DURATION AND HYPERTENSION IN THE MULTIETHNIC COHORT

2.1 Introduction

Hypertension, or high blood pressure, is a condition in which the force of blood pushing against the artery walls is higher than normal. According to the current guideline by the 2017 American College of Cardiology and the American Heart Association (ACC/AHA), hypertension is defined by a systolic blood pressure (SBP) above 130 mm Hg or diastolic blood pressure (DBP) above 80 mm Hg (Table 2) [49]. Previously, hypertension was defined by SBP above 140 mm Hg or DBP above 90 mm Hg.

Table 3. High blood pressure guidelines–adapted from Whelton et al. (2018).

Blood Pressure Category	**Systolic Blood Pressure**		**Diastolic Blood Pressure**
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension–Stage 1	130–139 mm Hg	or	80–89 mm Hg
Hypertension–Stage 2	≥140 mm Hg	or	≥90 mm Hg

2.1.1 Epidemiology of hypertension

In 2010, the global burden of hypertension among adults was estimated to be 31.1%, or approximately 1.39 billion people [50, 51]. In 2017, the U.S. prevalence was estimated to be approximately 44%, or about 104 million adults [52]. Among these adults, about one-third of individuals had stage 2 hypertension and it was estimated that only about a quarter of adults with hypertension have it under control [52].

Hypertension is one of the major public health concerns globally, and it is the leading modifiable risk factor for mortality [53]. In the U.S., approximately half a million deaths listed hypertension as a primary or contributing cause in 2017 [54]. Given that cardiovascular disease is the leading cause of death globally, it is likely that these diseases mediate the link between hypertension and early mortality [55]. The link between high blood pressure and cardiovascular disease is well established, and according to the Cardiovascular Research Using Linked Bespoke Studies and Electronic Health Records (CALIBER) study, high systolic and diastolic blood pressure was associated with an increased risk of intracerebral hemorrhage, subarachnoid hemorrhage, angina, and myocardial infarction [56], with those with SBP of 90–114 mm Hg and DBP of 60–74 mm Hg at lowest risk. SBP is also believed to be an independent risk factor even after adjusting for DBP [57, 58], but the independent effect of DBP is not well known [59].

2.1.2 Risk factors for hypertension

The burden of hypertension is known to differ by a variety of demographic factors, such as age, sex, and race/ethnicity. The risk of hypertension generally increases with age, as evidenced by a report on the 2011-2014 National Health and Nutrition Examination Survey (NHANES), which found that the prevalence of hypertension was 23%, 56%, and 78% among participants aged 18-44 years, 45-64 years, and ≥65 years, respectively [52]. This same report found that the prevalence was 47% in men and 42% in women. Ethnic differences were also reported, with the highest prevalence among non-Hispanic blacks (53%) and the lowest prevalence among Asian Americans (35%) and Hispanic whites (34%). These findings on ethnic differences may have been confounded by socioeconomic factors, as there is evidence of higher hypertension prevalence in low- and middle-income countries, compared to high-income countries [50].

Modifiable risk factors for hypertension include obesity, type 2 diabetes, an unhealthful diet, lack of physical activity, smoking, and alcohol consumption. Obesity is known to cause abnormal secretions of adipokines and free fatty acids, which can cause chronic vascular inflammation, oxidative stress, and sympathetic overdrive [60]. Commonly, in the U.S., hypertension prevalence is higher among obese adults, compared to those with a healthy weight BMI or considered overweight [52]. Diabetes and decreased glucose tolerance are also known risk factors for hypertension [16, 61], and according to the American Diabetes Association (ADA), approximately 70-80% of patients with type 2 diabetes also have hypertension [62].

There are many dietary components that are known to increase hypertension risk. According to the International Study of Macro/Micronutrients and Blood Pressure (INTERMAP) study, high energy, sodium, sugars, and cholesterol was positively correlated blood pressure [63]. In contrast, there are dietary components that have an inverse relationship with blood pressure, such as potassium, polyunsaturated fatty acids, and vitamin D consumption [64]. Today, dietary pattern interventions are one of the primary approaches to treating or preventing hypertension, and one of the dietary recommendations specific to reducing the risk of hypertension and cardiovascular disease is the Dietary Approaches to Stop Hypertension (DASH) dietary pattern [65]. The DASH is among many dietary recommendations in the U.S., and it is rich in fruits, vegetables, nuts, whole grains, and low-fat dairy items with a focus on reduced amounts of sodium, red and processed meats, and non-milk extrinsic sugars [66]. Evidenced by a meta-analysis from 17 randomized controlled trials (RCTs), adherence to the DASH diet has been associated with reductions in both SDP and DBP [67]. Similar results were reported from another meta-analysis published in 2020 that included 50 RCTs [68] and the authors reported reductions ranging from 3.20 to 7.62 mm Hg for SBP and 2.50 to 4.22 mm Hg for DBP [68].

However, there are also studies that concluded that this reduction is only evident in individuals that are already hypertensive [69].

Physical activity is also important in reducing hypertension risk, as there is generally an inverse relationship between the two [70, 71]. According to a report reviewing nine RCTs of adults, increases in moderate to vigorous physical activity led to a mean decrease of 5-10 and 1-6 mm Hg of systolic and diastolic blood pressures, respectively [70]. Even modest physical activity, such as a brisk 30-minute walk, has been associated with decreased risk of hypertension, according to an observational study of Japanese men [71].

The positive correlation between alcohol consumption and blood pressure has been supported by results of many studies [72-74], with some evidence that this relationship is modified by obesity [72]. A prospective cohort study conducted in China revealed that adults who were current drinkers were at a 65% higher risk of hypertension than those who either stopped drinking or never consumed alcohol [72]. A stratified analysis then showed that adults who were both current drinkers and obese were at 4.5 times the risk of incident hypertension, compared to those with having one of the two conditions. Another study examining a Chinese elderly population found that the effect of alcohol consumption is also modified by sodium intake [75]. A recent meta-analysis found that sex may also be an effect modifier of the alcohol-hypertension pathway [74]. The study showed that any amount of alcohol consumption gradually increased hypertension risk in men, but increased risk in women was only evident in those consuming more than 2 drinks per day.

Smoking is a well-established risk factor for hypertension and cardiovascular disease [76]. An analysis of a cohort of Japanese men found 13% increased odds of incident hypertension in smokers compared to non-smokers [77]. Similar results were replicated among a cohort of

women in the Women's Health Study, where a 10% increased risk was found among women smoking ≥15 cigarettes per day, compared to never smokers [78]. The risk of hypertension did not increase among former smokers and smokers who used 1 to 14 cigarettes per day. Smoking is also known to increase sleep latency and decrease overall sleep duration [79, 80].

2.1.3 Sleep as a Risk Factor for Hypertension

Sleep behaviors have recently been gaining attention as potential risk factors for hypertension, partially due to concerns of the increasing prevalence of sleep deprivation globally [1, 3]. While there seems to be a consensus that sleep-disordered breathing is a risk factor for hypertension [81], it is still unknown if the length of sleep is an independent risk factor. While many studies conclude that both sleep deprivation and excess sleep are risk factors for hypertension [31, 82], there are also findings suggesting that only one of these sleep categories are associated [32, 33], or that there is no association at all [83-85].

In the Sleep Heart Health Study (SHHS), a community-based observational study of middle-aged and elderly adults, participants reporting <6 hours of sleep per night were at 66% increased odds of hypertension compared to those reporting 7 to <8 hours of sleep per night, and >9 hours of sleep was associated with a 30% increase in odds [31]. A report based on the first National Health and Nutrition Examination Survey (NHANES I) also found a 60% increase in hypertension risk among young and middle-aged adults reporting ≤5 hours of sleep per night [32]. This association was not found among the elderly. Among participants reporting ≥9 hours of sleep per night, there was a small, but not statistically significant, increase in hypertension risk. The Coronary Artery Risk Development in Young Adults (CARDIA) study used actigraphy to objectively measure sleep duration and found a 37% increase in odds of incident hypertension

for each 1–hour reduction of sleep [33]. However, there are also studies that have found no association, whether they used subjective [84, 85] or objective [83] measurements of sleep.

The association between sleep duration and hypertension are also confounded by a variety of demographic characteristics and health risk factors. In a previous National Health Interview Surveys (NHIS) study, stratified analyses found that the association between sleep duration and prevalent hypertension was modified by age and sex [86]. Separating the population into three age groups, it was found that among men reporting <6 hours of sleep, the adjusted ORs for hypertension were 1.99 (95% CI: 1.52-2.60), 1.29 (95% CI: 1.05-1.60), and 1.22 (95% CI: 0.87-1.72), for 18-44 years, 45-64 years, and ≥65 years, respectively. The corresponding ORs for women were 2.13 (95% CI: 1.66-2.74), 1.01 (95% CI: 0.83-1.24), and 1.44 (95% CI: 1.16-1.80). Among male participants who reported ≥9 hours of sleep, the pattern was similar, with the strongest association seen among the youngest group. In women, however, the strongest association was seen among those aged 45-64 years (OR: 1.45, 95% CI: 1.06-1.98). Similar findings were reported in a Korean study, in which the odds of hypertension were higher among participants aged <65 years compared to older adults in both extremes of sleep duration [87]. Sex-specific results from the above NHIS study are reflected in other population-based studies. A report from the Whitehall II study studying British adults found that although there was a 72% higher odds of hypertension among women reporting short sleep, this association was absent among men in the population [88]. Higher odds of hypertension among women who are short sleepers have also been reported in a large meta-analysis of cross-sectional and prospective studies [89].

Ethnic differences in the sleep-hypertension relationship are extremely understudied. In a recent meta-analysis of 54 studies, ≤5, 6, and >9 hours of sleep, compared to 7–8, was a

predictor of incident hypertension regardless of ethnicity [90]. However, a significant association for moderately long sleep (>8 hours) was only detected among Asians. This lack of literature on the role of ethnicity is one of the primary motivations for conducting our study.

Studies examining the association between sleep duration and hypertension in different BMI groups are also scarce. In a recent study conducted using aggregate data from the 2013 BRFSS and 2007-2016 NHIS samples, increased risk of hypertension was seen among those sleeping ≤4 hours (OR: 1.86, 95% CI: 1.75-1.98), 5 hours (OR:1.56, 95% CI: 1.49-1.63), 6 hours (OR: 1.27, 95% CI: 1.23-1.30), 9 hours (OR: 1.19, 95% CI: 1.13-1.25), and ≥10 hours (OR: 1.41, 95% CI: 1.33-1.49) [91]. Stratified analyses were conducted by age, sex, and BMI groups, and no differences by age and sex were reported. Stratified analyses by BMI categories (normal, overweight, obese, and morbidly obese) found that the association between short sleep (≤4 hours) and hypertension was highest among those with normal BMI. Stronger associations in those with normal BMI and morbidly obese were seen in long sleepers (≥10 hours).

2.2 Objectives

The primary objective of this study was to estimate the association of self-reported sleep duration with prevalent and incident hypertension in the MEC study population. This study also aimed to investigate whether age, sex, ethnicity, and BMI as potential effect modifiers of this association.

The secondary objective of this study was to estimate the above association using prevalence and risk difference measures, instead of ratio measures, to better portray the public health impact of sleep duration on hypertension prevalence.

2.3 Methods

2.3.1 Study Population

The description and recruitment strategy of the MEC was described in section 1.3. This study used data from four MEC questionnaires (time points): Questionnaire 1 (1993–1996), questionnaire 2 (1998–2002), questionnaire 3 (2003–2006), and questionnaire 4 (2008–2012). Starting from the initial sample size of 215,903 participants, individuals were excluded from the prevalence analysis if they were not part of the five main ethnic groups or were missing information on sleep duration and hypertension status at baseline (Qx1). Participants were also excluded if they were missing information on height or weight and smoking. The final study sample to analyze the association between sleep duration and prevalent hypertension was 187,564 participants (Figure 1).

Further exclusions for the incidence analysis included participants who reported prevalent hypertension (from baseline Qx1) or did not participate in any of the follow-up questionnaires. The final study sample was 97,677 participants (Figure 2).

2.3.2 Exposure Variable – Sleep Duration

Information on sleep duration was obtained from the following question in the baseline MEC questionnaire: “On average, during the last year, how many hours in a day did you sleep (including naps)?”. Participants were given six response categories: ≤5, 6, 7, 8, 9, or ≥10 hours and the reference group was defined as 7 hours of sleep.

2.3.3 Outcome Variable – Hypertension

Prevalent hypertension cases were identified based on self-reported responses in the baseline (Qx1) MEC questionnaire, based on the following question, “Has your doctor ever told you that you had any of the following? (Mark all that apply)”. Incident cases were defined as any hypertension cases reported in Qx2, 3, and/or 4. Participants who did not participate in any of the follow-up questionnaires would have unknown hypertension status and were removed from the analytic sample. Participants who answered “Yes” in any of the follow-up questionnaires were considered incident cases. Participants were considered a non-case if they never answered “Yes” and answered “No” in at least one of the follow-up questionnaires.

2.3.4 Potential Confounders

Potential confounders were selected *a priori* based on their known associations with sleep duration and hypertension. Briefly, a variable is a potential confounder if 1) it is associated with the exposure, 2) it is not an effect of the exposure as it relates to the disease, and 3) it is associated with and predictive of the disease, but not predicted by the disease [92]. To avoid redundancy, Table 4 indicates the section(s) that describes evidence to suspect that the variable confounds the association between sleep duration and hypertension. Otherwise, the evidence is presented in this section.

Table 4. List of literature showing evidence of the association between the potential confounders and sleep/hypertension.

Variable	Sleep	Hypertension
Age	Section 1.1.1 [4] Section 2.3.4 [93]	Section 2.1.2 [52]
Sex	Section 1.1.1 [4] Section 2.3.4 [94]	Section 2.1.2 [52]
Ethnicity	Section 1.1.1 [4] Section 2.3.4 [29, 95, 96]	Section 2.1.2 [52]
Education Level	Section 2.3.4 [29, 97]	Section 2.1.2 [50] Section 2.3.4 [81, 84, 98]
BMI	Section 1.2 [16, 19-24, 99]	Section 2.1.2 [16, 52, 60-62]
Smoking status	Section 2.3.4 [79, 80]	Section 2.1.2 [76-78]
Alcohol consumption	Section 2.3.4 [100, 101]	Section 2.1.2 [72-75]
Caffeine consumption	Section 2.3.4 [102, 103]	Section 2.3.4 [104]
Dietary Quality (DASH)	Section 2.3.4 [105-107]	Section 2.1.2 [63-69, 108]
Physical activity	Section 2.3.4 [109-112]	Section 2.1.2 [70, 71]

The potential confounders considered were age at cohort entry (45-54, 55-64, ≥65 years), sex (male/female), ethnicity (White, African American, Native Hawaiian, Japanese American, and Latino), education level (≤12, 13–15, or ≥16 years), BMI (underweight <18.5 kg/m^2, normal weight 18.5–<25 kg/m^2, overweight 25–30 kg/m^2, and obese ≥30 kg/m^2), smoking status (never, past, or current smoker), smoking pack-years, alcohol consumption (below median and above or equal to median: men is <2.15 g/day and ≥2.15 g/day, women is 0 g/day and >0 g/day), caffeine consumption (<100, 100–<200, ≥200 mg/day), DASH dietary score (quartiles; 8-21, 22-24, 25-27, ≥28) and physical activity (quartiles: 0.1-1.43, 1.44-4.40, 4.41-8.86, ≥8.87 MET-hours in men; 0.1-1.43, 1.44-2.86, 2.87-6.20, ≥6.21 MET-hours in women).

According to published results based on the 2014 BRFSS data, the prevalence of short sleep duration differs by age, sex, and ethnicity [4]. In general, there is an inverse association between age and sleep duration, even after controlling for various social, demographic, and environmental factors [93]. In the U.S., the mean sleep duration is longer in women, although

differences are often small [94]. Differences in sleep behavior by ethnic groups is not well studied, although it appears that ethnic minorities are more likely to report shorter sleep durations [29, 95]. Ethnic minorities also are more likely to report sleep disturbances and poor sleep quality, although these associations may be confounded by socioeconomic status and access to health care [96].

In this study, education level was considered a proxy measure for an individual's socioeconomic status. There are currently no published studies that examined the independent association between education level and sleep duration. However, previous reports based on the MEC showed that the proportion of short sleepers (6 or less hours) was higher in groups with low (high school or less) or high (≥4 years of college) levels of education, compared to those in the middle (1-<4 years of college) [29, 97]. While this correlation was not explored further, it is possible that this observed relationship is an artifact of longer working hours associated with these two education groups. With regards to how educational attainment is associated with hypertension risk, these seems to be an inverse correlation between the two [81, 84], and there is also evidence of an association between lower educational attainment and poorer blood pressure control [98].

The association between BMI and sleep, as well as evidence that abnormal BMI is a risk factor for hypertension, was described previously. Expanding on the evidence linking sleep and BMI, this association is believed to be a complex, bidirectional relationship. The causal mechanism is not fully known, but it is hypothesized to involve appetite dysregulation, caused by lower leptin and higher ghrelin levels often seen in sleep-deprived individuals [99, 113]. In contrast, the relationship between excess sleep and higher BMI is unclear. It is possible that these individuals are generally less active and may spend more time at rest, which could be

misreported as sleep. In this study, BMI was obtained by taking the quotient of the participants' weight and height (kg/m^2), and these values were categorized based on CDC guidelines: underweight <18.5 kg/m^2, normal weight 18.5–<25 kg/m^2, overweight 25–30 kg/m^2, and obese ≥30 kg/m^2.

The association between alcohol consumption and the risk of developing hypertension is described in section 2.1.1 [72-74]. Alcohol use is also an important risk factor for sleep-disordered breathing, which is caused by alcohol-induced muscle relaxation [114]. A study based on the NHIS found that excessive alcohol consumption was associated with a higher prevalence of short sleep, and this association was stronger among black participants, compared to white participants [100]. A report based on a study conducted in Canada concluded similarly, where short sleep (≤6 hours) was associated with greater alcohol intake, exceeding the recommendations of sensible weekly alcohol intake [101]. Given the sex differences in the alcohol-hypertension relationship, participants were divided into low and high consumption categories based on sex-specific median consumption.

Caffeine is known to decrease sleep duration and depth of sleep by competing for adenosine receptors, one of the factors essential for initiating sleep [102]. There has been research showing that approximately 150 mg, approximately 1.5 cups of coffee, is enough to block approximately 50% of these receptors, leading to restlessness, longer sleep latency, enhanced nighttime wakefulness, and reduction of the duration and depth of sleep [103]. Caffeine consumption is also known to elevate blood pressure, and in the Singapore Chinese Health Study, a U-shaped association between cups of coffee and incident hypertension risk was found, with the lowest risk reported in those drinking 1 cup/day [104]. In this study, caffeine

consumption was divided into three categories: <100 mg/day, 100–<200 mg/day, and ≥200 mg/day.

The relationship between diet and sleep is a complex, bidirectional relationship. Evidence in literature suggest that both sleep duration [105] and sleep quality [115, 116] are associated with various dietary components (micronutrients, macronutrients, or specific foods) and eating behaviors [117]. In an Australian study consisting of young and middle-aged adults, an inverse association between the Dietary Quality Score (DQS) and sleep duration was found [105]. The study adjusted for key confounders such as age, socioeconomic status, education, physical activity, and BMI and found that each standard deviation increase in the DQS was associated with 13% and 21% reduced odds for short sleep among men and women, respectively. In a review of 16 cross-sectional studies conducted in the U.S., it was found that short sleep duration was consistently associated with higher total energy intake and higher total fat intake, as well as some evidence for lower fruit intake and lower dietary scores [107]. In contrast, a study conducted in a population of young to elderly adults in the UK found that long sleep (>8 hours) was associated with a lower healthy dietary pattern score [106].

The DASH adherence score used in this study has been previously described [118]. Briefly, energy-adjusted consumption for each of the eight food groups was calculated for each individual and this was used to determine the quintile for each food group. For the five recommended food groups, those in the highest quintile received a score of 5, while those in the lowest quintile received a 1. For the three food groups to be limited, reverse scoring was used, where the highest quintile received a score of 1. Therefore, the DASH accordance score for an individual had a potential range of 8 to 40 points.

Physical activity is considered one of many therapeutic approaches in increasing sleep duration and improving sleep quality [110]. However, the association between sleep and physical activity is more complex and improvement in one can lead to an improvement in the other, creating a feedback loop [109]. It has been shown repeatedly in literature that moderate- to vigorous-intensity physical activity (MVPA) is associated with shorter total sleep time, greater sleep efficiency, and less sleep fragmentation [111, 112]. In this study, physical activity was measured using metabolic equivalent of tasks (METs) of MVPA per day. Briefly, the MET is a ratio measure of the energy cost associated with the activity in comparison to the resting metabolic rate (sitting quietly). Compared to one MET, equivalent to sitting still, a brisk walk, bicycling, and jogging have scores of 3, 5.5, and 7, respectively. In this study, MET-hours of MVPA per day was divided into sex-specific quartiles for analysis.

Based on the known associations between sleep duration, hypertension, and confounding variables, the following causal diagram was proposed (Figure 3).

2.3.5 Statistical Analysis

Descriptive parameters of the population characteristics were shown as means and standard deviations for continuous variables and proportions for categorical variables. A one-way analysis of variance (ANOVA) was used to test differences in the means of baseline continuous variables across categories of sleep duration. For categorical variables, the χ^2 test was performed to compare distributions of baseline variables across categories of sleep duration.

Prevalence ratios (PRs) and 95% confidence intervals (CIs) for the association between prevalent hypertension and sleep duration were estimated using a multivariable log-binomial model, with 7 hours of sleep as the reference group. Risk ratios (RRs) and 95% CIs were also estimated using a multivariable log-binomial model for incident hypertension. These models

were adjusted for all potential confounders (section 2.3.4). Stratified analyses by age, sex, ethnicity, and BMI, each adjusted for all other variables, were also presented. For secondary analysis, prevalence and risk differences, as well as 95% CIs, were estimated to obtain the mean number of excess hypertension cases associated with each sleep category (compared to the reference 7 hours).

Statistical significance was determined *a priori* as $p < 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Log-binomial models were conducted using the PROC GENMOD procedure in SAS, specifying 'binomial' as the distribution and 'log' as the link function to obtain ratio estimates. The 'identity' link function was used to estimate difference measures.

2.4 Results

2.4.1 Demographics

At baseline (1993-1996), there were 73,291 prevalent hypertension cases among 187,564 participants (Figure 1). During the study period between 1993 and 2012, 37,050 incident hypertension cases were identified among 97,267 participants (Figure 2). The majority of participants reported 6-8 hours of sleep per day, and only 19% of the participants reported ≤5, 9, or ≥10 hours of sleep (Table 5). The ethnic distribution in the study sample was 25.6% white, 15.9% African American, 7.4% Native Hawaiian, 29.6% Japanese American, and 21.5% Latino. The proportion of those reporting ≤5 hours was highest among African American participants (16.1%), followed by Native Hawaiian (14.3%) and Latino (10.5%) participants. The same ethnic groups were more likely to report ≥10 hours, compared to the white and Japanese participants. Japanese Americans were the least likely to report long sleep (9 & ≥10 hours). In summary, participants reporting short sleep were more likely to be older, female, be less

educated, be obese, consume less alcohol and caffeine, have lower dietary scores, and exercise less. Participants reporting long sleep were more likely to be older, be male, be less educated, be obese, be current smokers, consume less alcohol, and exercise less. Participants with missing information on education level, alcohol consumption, caffeine consumption, DASH score, and physical activity were more likely to report extreme short and long sleep, compared to those without missing information.

2.4.2 Prevalent hypertension

After adjustment for confounding variables, there was a small, U-shaped association between sleep duration and prevalent hypertension. The highest estimates were observed among participants reporting ≤5 (PR: 1.07, 95% CI: 1.05-1.08), 9 (PR: 1.06, 95% CI: 1.04-1.08), and ≥10 hours (PR: 1.08, 95% CI: 1.05-1.11) of sleep (Table 6). There was effect modification by age, ethnicity, and BMI, but not sex. Slightly higher estimates among the youngest participants (45-54 years) were observed in those reporting ≤5, 6, and ≥10 hours of sleep. Among those reporting ≤5 hours of sleep, lower estimates were observed among African American (PR: 1.04, 95% CI: 1.01-1.07) and Japanese American (PR: 1.04, 95% CI: 1.00-1.08) participants compared to other ethnic groups. African American participants also had the lowest PR in the ≥10-hour group (PR: 1.01, 95% CI: 0.96-1.06), and all other ethnic groups experienced at least a 10% elevation in hypertension prevalence. When participants were stratified by BMI categories, the only difference was observed among underweight participants. Among those who reported ≤5 hours of sleep, those who were underweight had a PR of 1.17 (95% CI: 0.97-1.42), compared to 1.09 (95% CI: 1.05-1.13) in participants with normal BMI. Higher estimates in underweight participants were also seen in those reporting 9 hours of sleep (PR: 1.23, 95% CI: 0.97-1.56).

Prevalence differences (PDs) were also estimated to obtain the mean number of excess hypertension cases associated with each sleep category. Approximately 31 (95% CI: 23-39), 23 (95% CI: 13-32), and 42 (95% CI: 27-57) excess hypertension cases per 1,000 participants were associated with sleeping ≤5, 9, and ≥10 hours, respectively (Table 7). Stratified analyses by age groups revealed a decreasing trend in the number of excess cases associated with ≤5 and 6 hours of sleep with increasing age. However, among participants reporting ≥10 hours of sleep, the oldest group had higher number of excess cases (PD: 0.053, 95% CI: 0.031-0.075) compared to the youngest group (PD: 0.032, 95% CI: 0.005-0.059). According to stratified analyses by ethnic groups, white (PD: 0.054, 95% CI: 0.035-0.073) and Native Hawaiian (PD: 0.052, 95% CI: 0.026-0.078) participants had the highest number of excess hypertension cases associated with ≤5 hours of sleep, while the number of excess cases was lowest among Japanese Americans (PD: 0.014, 95% CI: -0.002-0.030). The estimated number of excess cases associated with ≥10 hours of sleep was highest among Native Hawaiian (PD: 0.067, 95% CI: 0.018-0.116) and Japanese American (PD: 0.067, 95% CI: 0.030-0.103), and lowest in African Americans (PD: 0.005, 95% CI: -0.025-0.036). Similar to the trends seen with PRs (Table 6), there were no clear patterns in differences by BMI.

2.4.3 Incident hypertension

The fully adjusted RRs did not indicate higher risk of hypertension in any sleep categories compared to 7 hours of sleep (Table 8). There was also no evidence of effect modification of this association by age, sex, ethnicity, or BMI. Examining differences in risk estimates, only 6 hours of sleep (RD: 0.014, 95% CI: 0.006-0.022) appeared to be associated with a small elevation in the number of excess incident hypertension cases (Table 9). Effect

modification by age, sex, ethnicity, or BMI was also not detected when examining risk differences.

2.5 Discussion

In this study based on a large, ethnically diverse population, a weak association between prevalent hypertension and sleep duration on the additive and multiplicative scales was detected. The magnitude of association found in our study was different from that of previous studies, such as the Sleep Heart Health Study [31] and the NHANES I [32] study. In the Sleep Heart Health Study, there was 66% increased odds of prevalent hypertension among participants reporting <6 hours of sleep and 30% increased odds in those reporting >9 hours of sleep [31]. Similar estimates were reported in the NHANES I study among short sleepers, but not long sleepers [32]. This discrepancy in the estimates may have been due to differences in the variable adjustments and estimates from literature may have been inflated due to their usage of odds ratios.

In this study, sleep duration was not associated with incident hypertension. Similar findings were reported from a population-based study of older adults in Spain, in which the authors did not see any association with prevalent or incident hypertension [84]. Null results were also obtained from the Buffalo Cardio-Metabolic Occupational Police Stress study, where sleep parameters were measured by actigraphy [83]. Interestingly, there was a strong, unadjusted association between sleep duration and incident hypertension, but there was no association after adjustments for demographic factors, alcohol use, physical activity, smoking status, cigarette smoking, depressive symptoms, shift work, BMI, obstructive sleep apnea, and caloric intake.

Our findings were not consistent with our hypothesis, which was based on previous findings and known biological mechanisms linking sleep to hypertension. For example, sleep

deprivation is often associated with sleep disturbances, such as frequent arousals, that is known to cause an overactivity of the sympathetic nervous system [119]. This overactivity is correlated with the absence of 'nocturnal dipping', which refers to a decrease in blood pressure during sleep [120]. Sleep deprivation is also associated with other physiological risk factors for hypertension, such as increased intima-media thickness of the artery [121], increased artery calcification [122], higher cortisol and cholesterol levels [123], decreased glucose tolerance [124], and increased production of proinflammatory cytokines [125]. Excess sleep has also been found to be associated with a variety of cardiovascular risk factors, such as inflammation [126], atherosclerosis [127], arterial stiffness [128], and sleep apnea [83]. We present several hypotheses as to why our findings differed from our expectations. First, as previously mentioned, many previous literatures reported odds ratio, instead of prevalence or risk ratios, as their estimate of association, which is often inflated for non-rare outcomes. Second, any associations seen in previous literature, or our current study may be biased due to unmeasured confounders. In our study, we were unable to adjust for potential confounders such as the usage of sleep medications, psychosocial stress, other indicators of socioeconomic status, and other medical conditions. Third, our methodology in ascertaining hypertension cases through self-reported questionnaires without validation through physician diagnosis, blood pressure measurements, or medication use history may have affected our results. In a previous cohort study in Iran, the prevalence of hypertension based on self-reporting was 16.8% and 15.7% based on medical history and blood pressure measurements [129]. The sensitivity and specificity of self-reported hypertension was 75.5% and 96.4%, respectively. Assuming non-differential misclassification, these false positive and false negatives would result in biasing our estimates towards the null. In a meta-analysis of 22 studies conducted in 2018, self-reported hypertension underestimated the

prevalence compared to objective measures [130]. The authors reported similar specificity as the Iran study but found much lower sensitivity of 42.1%. This issue with recall bias, combined with changing diagnostic criteria during the study period, may also explain differences we saw between our cross-sectional and longitudinal analysis.

The present study examined the role of age, sex, ethnicity, and BMI as effect modifiers of the association between sleep duration and hypertension. Results from both prevalence and incidence analysis revealed small differences by age, but we do not believe this difference is clinically significant. Previous reports examining similar age groups are scarce and have inconsistent results. For example, our findings were similar to a report of the 2007-2009 NHIS, in which the adjusted ORs for hypertension among short sleeping (<6 hours) men was 1.29 and 1.22 for those aged 45-64 years and ≥65 years, respectively [86]. However, different results were obtained from short-sleeping women, with ORs of 1.01 and 1.44 for the same age groups. A Korean study also found small differences in the association by age, in which the odds of hypertension associated with ≤5 hours of sleep was higher among those aged <65 years (OR: 1.31), compared to those aged ≥65 years (OR: 1.15) [87]. Finally, a study based on the 2014-2017 NHIS found little difference in the association between those aged 45-64 years (OR: 1.06) and ≥65 years (OR: 1.09) [131].

Our study also found no sex differences in the association between sleep and hypertension. This finding is different from many previous reports, many of which found stronger associations in women [88, 89, 132]. Likewise, our study also did not find clinically significant differences by ethnicity. However, an interesting finding from this analysis was that we did not detect any increased prevalence or risk of hypertension in any sleep categories among African American participants. In all other ethnic groups, we found that extreme short and long

sleep was associated with an increased prevalence of hypertension. This finding is unique, as there are no previous studies investigating ethnic differences of the sleep-hypertension relationship.

Finally, our study did not find any differences the sleep-hypertension association by BMI. Although we observed that estimates among underweight participants differed in some sleep categories, we hesitate to conclude any clinical significance in this difference due to the wide confidence intervals in this group. There were two prior reports that investigated the role of BMI in the sleep-hypertension relationship. The first study is based on the 2014-2017 NHIS study discussed previously, and they also found that the highest association between short sleep and prevalent hypertension in underweight participants (OR: 1.37) [131]. However, the study results differed in that there was difference across the other BMI groups as well, whereas our study did not see differences between the normal weight, overweight, and obese participants. Another study that investigated the joint effect of sleep and obesity found that, compared to participants with BMI less than 30 kg/m^2 and reporting 6 or more hours of sleep, those who reported sleep <6 hours and were obese were at a 372% increased risk of hypertension [83].

2.5.1 Strengths and Limitations

The present study was based on a large ethnically diverse population with an extensive questionnaire, thereby allowing numerous confounding variables to be considered in the analysis. This study is the first to investigate age, sex, ethnicity, and BMI as potential effect modifiers of the sleep-hypertension relationship. Majority of previous studies have reported odds ratios as the measure of association, which can often overestimate prevalence and risk. We reported prevalence and risk ratios, which are less biased estimates when studying cross-sectional and longitudinal data.

One of the limitations to this study is that information on sleep duration and key covariates were self-reported at one point in time, and there were no objective measurements to validate the responses. For example, self-reported sleep duration could differ from actual physiological sleep and could be over-reported. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, it was found that the overall correlation between objective (actigraphy) and subjective sleep measurements was only 0.47, with participants who slept an average of 5 hours over-reporting their mean sleep duration by 1.2 hours [133]. In contrast, there are also studies that reported small differences between subjective and objective measurements of sleep [134, 135]. Sleep duration obtained in this study was not specific to nocturnal sleep and reflected the number of hours over a 24-hour period, thus making our results difficult to compare with previous literature. Another limitation in our study is the self-reported nature of hypertension status. In our incidence analysis, this may have introduced selection bias, because we may have erroneously selected for participants that were misclassified on hypertension status. However, we do not believe that any misclassification of hypertension status is related to sleep duration, and therefore our estimates are conservative. Another concern is our inability to distinguish the severity of hypertension as actual measurements were not available. Given the high prevalence and incidence of the condition in this population, it is likely that many cases are mild and the association with sleep duration may not be present among participants with incidental diagnosis of slightly elevated blood pressure. Our study was not able to include any information regarding sleep quality, sleep disorders, and the usage of sleep medications, which may be potential confounders. In addition, other factors such as psychosocial stress, employment status and job types, and pre-existing medical conditions are other confounders we could not account for.

2.6 Conclusion

In conclusion, sleeping shorter or longer than 7 hours was weakly associated with increased prevalence of hypertension among middle-aged and elderly adults in L.A. and Hawaii. Contrary to our hypothesis, this association did not differ by age, sex, ethnicity, or BMI. Our findings have several important public health implications. First, our findings suggest that the risk of hypertension associated with poor sleep, if any, is consistent regardless of demographic factors. Second, the absence of any association in our study suggest that the length of sleep may not be an independent risk factor for hypertension, and more research needs to be conducted to better characterize sleep behaviors as potential risk factors for disease. Third, discrepancies in our findings compared to previous literature emphasizes the complexity of the sleep-hypertension mechanism, and that making any causal inferences will be difficult until more research is conducted on the interactions between sleep behaviors, hypertension, and any associated risk factors.

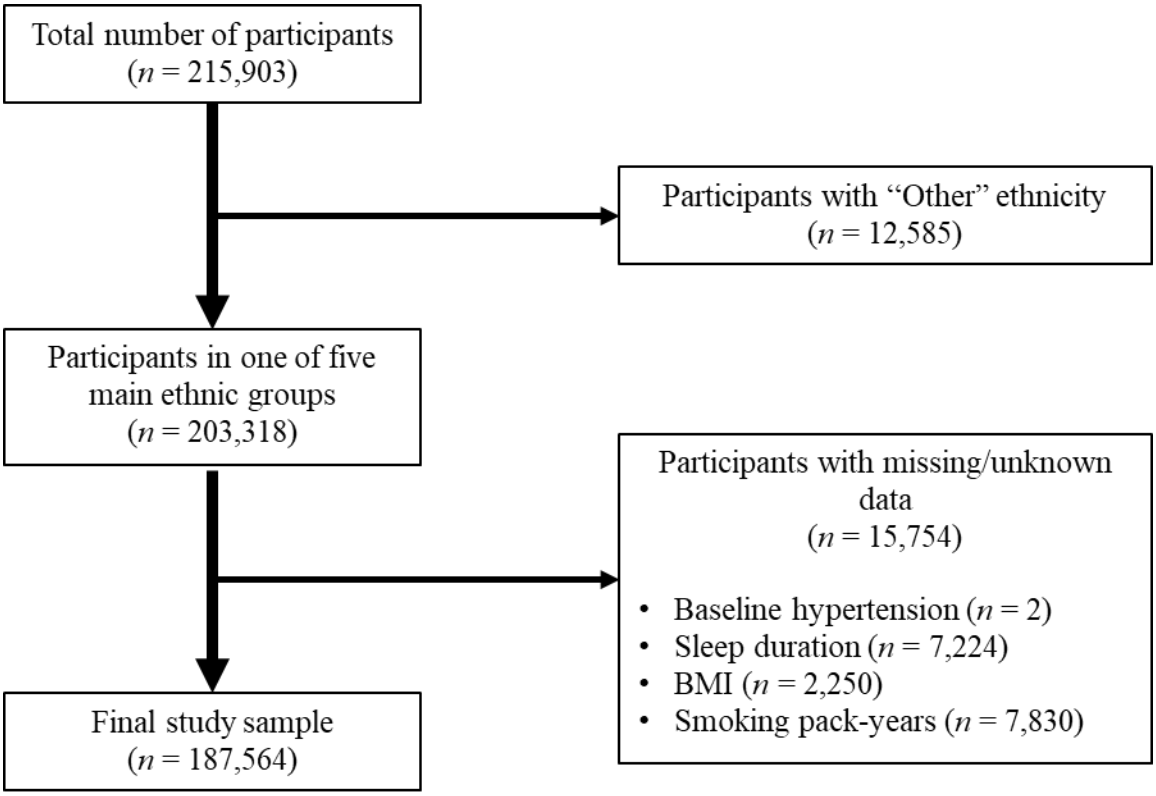

Figure 1. Exclusion criteria to analyze the association between sleep duration and prevalent hypertension in the MEC, 1993–1996.

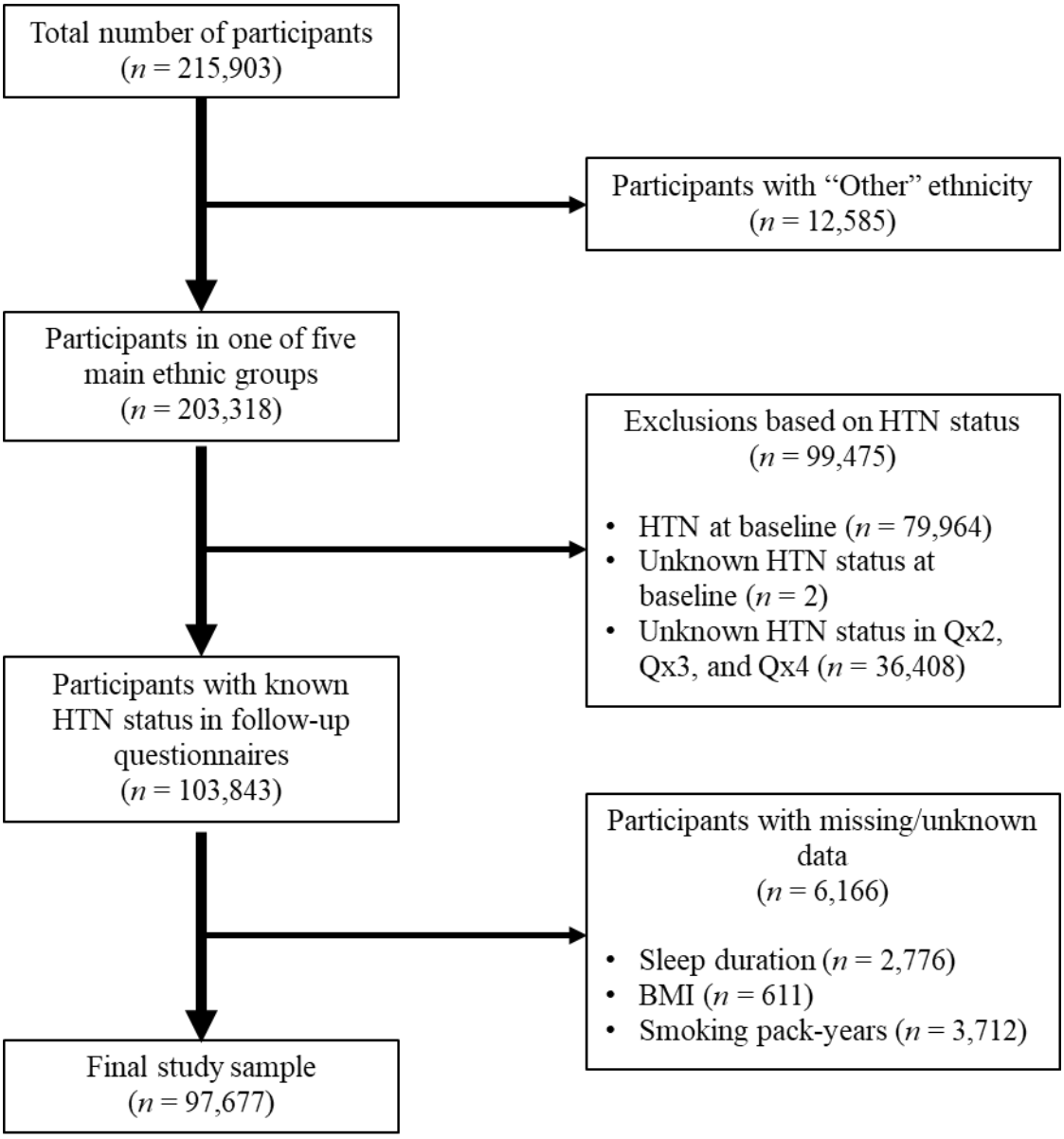

Figure 2. Exclusion criteria to analyze the association between sleep duration and incident hypertension in the MEC, 1993–2012.

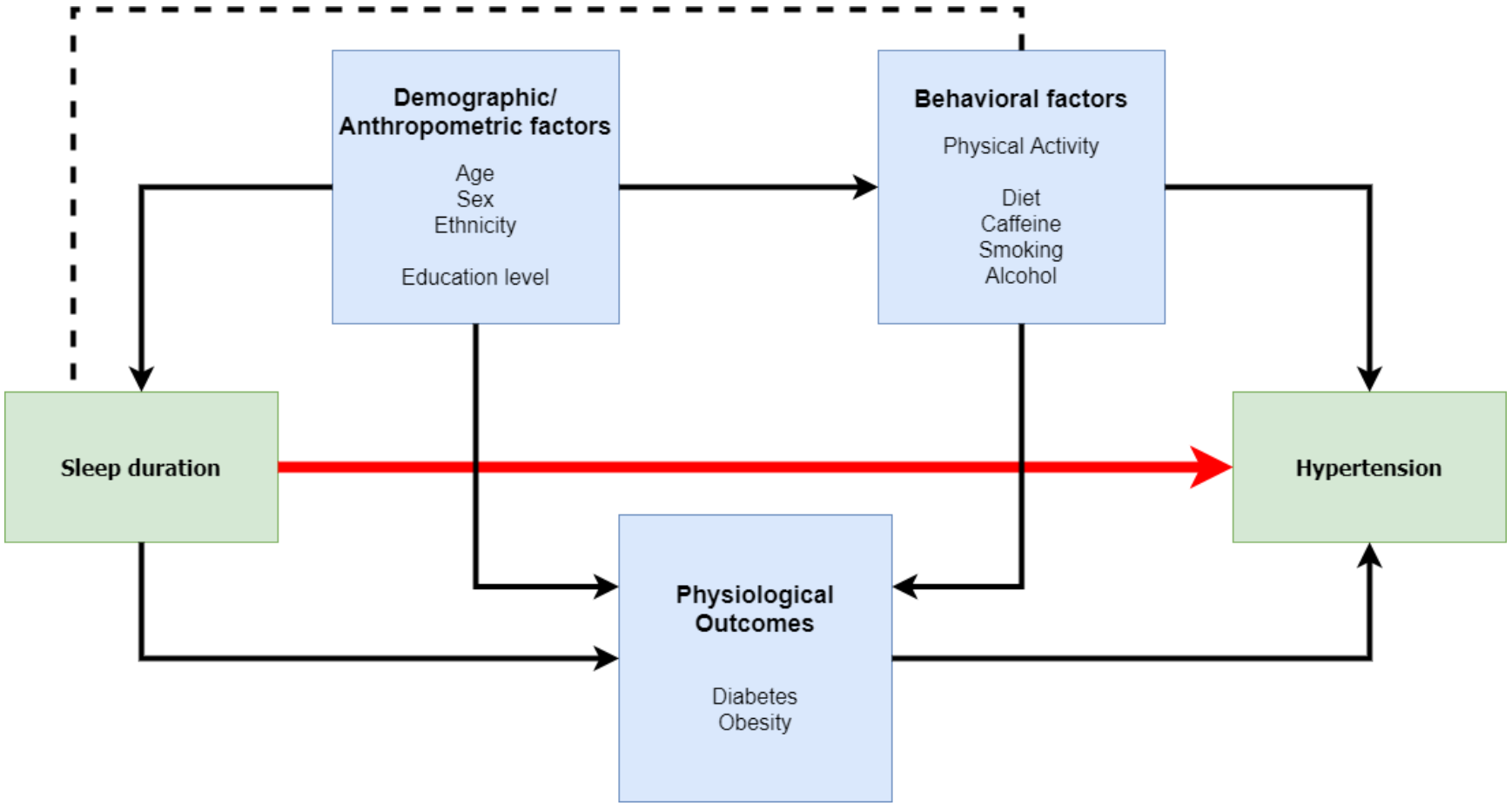

Figure 3. Causal diagram representing the relationship between sleep duration, hypertension, and confounding variables. Dotted lines represent an association between factors and arrows represent causal direction.

Table 5. Demographic characteristics of participants at the baseline questionnaire (Aim 1), MEC, 1993-1996.

		Sleep Duration (Hours)						
	All (*n*)	**≤5**	**6**	**7**	**8**	**9**	**≥10**	***p*[c]**
Number of Participants	187,564	18,317 (9.8%)	45,677 (24.4%)	58,954 (31.4%)	47,350 (25.2%)	12,819 (6.8%)	4,447 (2.4%)	
Age (years)[a]								<0.0001
45-54	60,158	5,533 (9.2%)	15,875 (26.4%)	20,066 (33.4%)	14,093 (23.4%)	3,448 (5.7%)	1,143 (1.9%)	
55-64	62,354	6,112 (9.8%)	15,105 (24.2%)	19,814 (31.8%)	15,807 (25.3%)	4,094 (6.6%)	1,422 (2.3%)	
≥65	65,052	6,672 (10.3%)	14,697 (22.6%)	19,074 (29.3%)	17,450 (26.8%)	5,277 (8.1%)	1,882 (2.9%)	
Sex[a]								<0.0001
Male	85,610	7,361 (8.6%)	20,793 (24.3%)	27,109 (31.7%)	22,032 (25.7%)	6,080 (7.1%)	2,235 (2.6%)	
Female	101,954	10,956 (10.8%)	24,884 (24.4%)	31,845 (31.2%)	25,318 (24.8%)	6,739 (6.6%)	2,212 (2.2%)	
Ethnicity[a]								<0.0001
White	47,504	2,538 (5.3%)	9,061 (19.1%)	16,421 (34.6%)	14,519 (30.6%)	4,039 (8.5%)	926 (1.9%)	
African American	30,132	4,855 (16.1%)	7,708 (25.6%)	7,417 (24.6%)	6,906 (22.9%)	2,158 (7.2%)	1,088 (3.6%)	
Native Hawaiian	13,580	1,943 (14.3%)	3,686 (27.2%)	3,749 (27.6%)	2,961 (21.8%)	844 (6.2%)	397 (2.9%)	
Japanese American	54,502	4,585 (8.4%)	16,076 (29.5%)	19,073 (35.0%)	11,554 (21.2%)	2,496 (4.6%)	718 (1.3%)	
Latino	41,846	4,396 (10.5%)	9,146 (21.9%)	12,294 (29.4%)	11,410 (27.3%)	3,282 (7.8%)	1,318 (3.1%)	
Education[a]								<0.0001
≤12 years	80,897	9,868 (12.2%)	18,561 (23.0%)	22,758 (28.1%)	20,902 (25.8%)	6,139 (7.6%)	2,669 (3.3%)	
13-15 years	55,639	5,000 (9.0%)	14,260 (25.6%)	17,826 (32.0%)	13,711 (24.7%)	3,727 (6.7%)	1,115 (2.0%)	
≥16 years	50,291	3,342 (6.6%)	12,702 (25.3%)	18,184 (36.2%)	12,537 (24.9%)	2,898 (5.8%)	628 (1.2%)	
Missing	737	107 (14.5%)	154 (20.9%)	186 (25.2%)	200 (27.1%)	55 (7.5%)	35 (4.8%)	
BMI (kg/m^2)[a,c]								<0.0001
Underweight	3,321	366 (11.0%)	845 (25.5%)	1,009 (30.4%)	781 (23.5%)	217 (6.5%)	103 (3.1%)	
Normal	74,992	6,046 (8.1%)	18,039 (24.1%)	25,588 (34.1%)	19,150 (25.5%)	4,831 (6.4%)	1,338 (1.8%)	
Overweight	71,903	7,017 (9.8%)	17,737 (24.7%)	22,236 (30.9%)	18,316 (25.5%)	4,936 (6.8%)	1,661 (2.3%)	
Obese	37,348	4,888 (13.1%)	9,056 (24.2%)	10,121 (27.1%)	9,103 (24.4%)	2,835 (7.6%)	1,345 (3.6%)	
Smoking status[a]								<0.0001
Never	84,086	8,478 (10.1%)	20,921 (24.9%)	27,098 (32.2%)	20,763 (24.7%)	5,171 (6.1%)	1,655 (2.0%)	
Yes, quit	73,157	6,532 (8.9%)	17,331 (23.7%)	22,987 (31.4%)	19,097 (26.1%)	5,421 (7.4%)	1,789 (2.5%)	
Yes, current	30,321	3,307 (10.9%)	7,425 (24.5%)	8,869 (29.3%)	7,490 (24.7%)	2,227 (7.3%)	1,003 (3.3%)	

Smoking pack-years[b]								<0.0001
Alcohol consumption (g/day)[a]								<0.0001
<2.15 (men), 0 (women)	101,604	10,876 (10.7%)	25,542 (25.1%)	30,905 (30.4%)	24,981 (24.6%)	6,700 (6.6%)	2,600 (2.6%)	
≥2.15 (men), >0 (women)	79,063	6,338 (8.0%)	18,455 (23.3%)	26,338 (33.3%)	20,725 (26.2%)	5,658 (7.2%)	1,549 (2.0%)	
Missing	6,897	1,103 (16.0%)	1,680 (24.4%)	1,711 (24.8%)	1,644 (23.8%)	461 (6.7%)	298 (4.3%)	
Caffeine consumption (mg/day)[a]								<0.0001
<100	93,691	9,652 (10.3%)	22,622 (24.1%)	28,955 (30.9%)	23,775 (25.4%)	6,431 (6.9%)	2,256 (2.4%)	
100-<200	37,024	3,329 (9.0%)	8,732 (23.6%)	11,764 (31.8%)	9,717 (26.3%)	2,649 (7.1%)	833 (2.2%)	
≥200	49,952	4,233 (8.5%)	12,643 (25.3%)	16,524 (33.1%)	12,214 (24.4%)	3,278 (6.6%)	1,060 (2.1%)	
Missing	6,897	1,103 (16.0%)	1,680 (24.4%)	1,711 (24.8%)	1,644 (23.8%)	461 (6.7%)	298 (4.3%)	
DASH score[a]								<0.0001
8-21	51,724	5,637 (10.9%)	13,484 (26.1%)	15,686 (30.3%)	12,185 (23.6%)	3,380 (6.5%)	1,352 (2.6%)	
22-24	44,226	4,324 (9.8%)	10,835 (24.5%)	13,889 (31.4%)	11,089 (25.1%)	3,027 (6.8%)	1,062 (2.4%)	
25-27	43,244	3,941 (9.1%)	10,229 (23.7%)	13,937 (32.2%)	11,181 (25.9%)	3,044 (7.0%)	912 (2.1%)	
≥28	41,473	3,312 (8.0%)	9,449 (22.8%)	13,731 (33.1%)	11,251 (27.1%)	2,907 (7.0%)	823 (2.0%)	
Missing	6,897	1,103 (16.0%)	1,680 (24.4%)	1,711 (24.8%)	1,644 (23.8%)	461 (6.7%)	298 (4.3%)	
Physical activity (MET-hours/day)[a,d]								<0.0001
0.1-1.43 (men), 0.1-1.43 (women)	54,041	6,646 (12.3%)	13,080 (24.2%)	15,085 (27.9%)	13,330 (24.7%)	3,974 (7.3%)	1,926 (3.6%)	
1.44-4.40 (men), 1.44-2.86 (women)	39,113	3,693 (9.4%)	9,851 (25.2%)	12,455 (31.8%)	9,711 (24.8%)	2,637 (6.8%)	766 (2.0%)	
4.41-8.86 (men), 2.87-6.20 (women)	42,539	3,423 (8.1%)	10,544 (24.8%)	14,447 (34.0%)	10,661 (25.1%)	2,730 (6.4%)	734 (1.7%)	
≥8.87 (men), ≥6.21 (women)	43,663	3,475 (8.0%)	10,294 (23.6%)	14,647 (33.5%)	11,483 (26.3%)	2,966 (6.8%)	798 (1.8%)	
Missing	8,208	1,080 (13.2%)	1,908 (23.2%)	2,320 (28.3%)	2,165 (26.4%)	512 (6.2%)	223 (2.7%)	

[a]n (row %).
[b]mean ± SD.
[c]underweight (<18.5 kg/m^2), normal weight (18.5-<25 kg/m^2), overweight (25–30 kg/m^2), and obese (≥30 kg/m^2).
[d]METs for moderate and vigorous activity per day.
[e]p values calculated by analysis of variance and χ^2 test.

Table 6. Estimated associations (prevalence ratios [PRs] and 95% confidence intervals [CIs]) between self-reported sleep duration and prevalent hypertension; overall model and stratified models by age, sex, ethnicity, and BMI.

		Hours of Sleep					
		≤5	**6**	**7**	**8**	**9**	**≥10**
	No. of events/No. of participants	8,449/18,317	18,088/45,677	21,217/58,954	18,038/47,350	5,349/12,819	2,150/4,447
		PR (95% CI)[a]					
Overall	73,291/187,564	1.07 (1.05-1.08)	1.03 (1.01-1.04)	1.00	1.02 (1.01-1.03)	1.06 (1.04-1.08)	1.08 (1.05-1.11)
Age							
45-54	16,885/60,158	1.12 (1.07-1.16)	1.07 (1.04-1.11)	1.00	1.01 (0.98-1.05)	1.06 (1.01-1.12)	1.14 (1.06-1.23)
55-64	24,828/62,354	1.07 (1.04-1.11)	1.02 (1.00-1.05)	1.00	1.03 (1.01-1.06)	1.07 (1.03-1.11)	1.09 (1.03-1.14)
≥65	31,578/65,052	1.04 (1.02-1.07)	1.01 (0.99-1.03)	1.00	1.01 (0.99-1.03)	1.06 (1.03-1.09)	1.09 (1.05-1.13)
Sex							
Male	34,487/85,610	1.06 (1.03-1.08)	1.05 (1.03-1.07)	1.00	1.03 (1.01-1.06)	1.05 (1.02-1.08)	1.08 (1.04-1.12)
Female	38,804/101,954	1.07 (1.04-1.09)	1.01 (0.99-1.03)	1.00	1.01 (0.99-1.03)	1.07 (1.04-1.10)	1.09 (1.05-1.12)
Ethnicity							
White	13,866/47,504	1.15 (1.10-1.21)	1.10 (1.06-1.14)	1.00	1.04 (1.01-1.08)	1.09 (1.04-1.15)	1.15 (1.07-1.24)
African American	16,724/30,132	1.04 (1.01-1.07)	0.99 (0.96-1.02)	1.00	1.00 (0.97-1.02)	1.04 (1.01-1.08)	1.01 (0.96-1.06)
Native Hawaiian	6,057/13,580	1.10 (1.04-1.16)	1.03 (0.98-1.09)	1.00	1.08 (1.02-1.13)	1.09 (1.01-1.16)	1.11 (1.02-1.20)
Japanese American	21,769/54,502	1.04 (1.00-1.08)	1.01 (0.99-1.04)	1.00	1.03 (1.01-1.06)	1.03 (0.99-1.08)	1.10 (1.04-1.16)
Latino	14,875/41,846	1.10 (1.06-1.15)	1.05 (1.01-1.09)	1.00	0.99 (0.95-1.02)	1.08 (1.03-1.13)	1.12 (1.05-1.20)
BMI (kg/m^2)							
Underweight	781/3,321	1.17 (0.97-1.42)	1.05 (0.89-1.24)	1.00	1.01 (0.85-1.21)	1.23 (0.97-1.56)	0.91 (0.66-1.27)
Normal	22,137/74,992	1.09 (1.05-1.13)	1.03 (1.00-1.06)	1.00	1.02 (0.99-1.05)	1.06 (1.01-1.11)	1.15 (1.08-1.23)
Overweight	29,839/71,903	1.08 (1.05-1.11)	1.03 (1.01-1.05)	1.00	1.02 (0.99-1.04)	1.08 (1.04-1.12)	1.11 (1.05-1.16)
Obese	20,534/37,348	1.06 (1.03-1.09)	1.02 (0.99-1.05)	1.00	1.02 (1.00-1.05)	1.05 (1.01-1.08)	1.07 (1.02-1.12)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, and DASH score.

Table 7. Estimated associations (prevalence differences [PDs] and 95% confidence intervals [CIs]) between self-reported sleep duration and prevalent hypertension on an additive scale; overall model and stratified models by age, sex, ethnicity, and BMI.

	Hours of Sleep					
	≤5	**6**	**7 (ref)**	**8**	**9**	**≥10**
			PD (95% CI)[a]			
Total Population						
Fully adjusted[b]	31 (23, 39)	12 (6, 18)	0	6 (0, 12)	23 (13, 32)	42 (27, 57)
Age Group[c]						
45-54	44 (31, 57)	17 (9, 25)	0	1 (-7, 8)	13 (-1, 27)	32 (5, 59)
55-64	36 (23, 50)	11 (2, 21)	0	12 (2, 22)	30 (14, 46)	50 (24, 75)
≥65	26 (13, 40)	7 (-3, 18)	0	6 (-4, 16)	30 (15, 45)	53 (31, 75)
Sex[c]						
Male	25 (13, 38)	19 (11, 28)	0	9 (0, 17)	20 (7, 33)	44 (23, 64)
Female	34 (24, 45)	6 (-2, 14)	0	5 (-3, 13)	28 (15, 41)	46 (25, 67)
Ethnicity[c]						
White	54 (35, 73)	23 (13, 34)	0	7 (-2, 16)	18 (3, 33)	51 (20, 83)
African American	26 (9, 43)	-3 (-19, 12)	0	-2 (-18, 14)	28 (5, 50)	5 (-25, 36)
Native Hawaiian	52 (26, 78)	17 (-5, 38)	0	28 (6, 51)	38 (2, 75)	67 (18, 116)
Japanese American	14 (-2, 30)	5 (-5, 15)	0	11 (0, 23)	18 (-2, 38)	67 (30, 103)
Latino	38 (22, 54)	19 (7, 31)	0	-5 (-17, 6)	27 (9, 45)	45 (18, 72)
BMI[c]						
Underweight	47 (-4, 98)	6 (-28, 40)	0	-9 (-44, 27)	30 (-33, 93)	-18 (-105, 68)
Normal	32 (19, 44)	9 (2, 17)	0	3 (-5, 10)	12 (-1, 25)	40 (14, 65)
Overweight	40 (27, 53)	17 (8, 27)	0	7 (-2, 16)	34 (19, 49)	52 (28, 76)
Obese	37 (21, 54)	16 (2, 29)	0	10 (-4, 24)	29 (9, 49)	50 (23, 76)

[a]excess number of prevalent hypertension cases (per 1,000 individuals) associated with sleep categories compared to the referent 7-hour group.

[b]adjusted for age, sex, ethnicity, education level, BMI, smoking status, smoking pack-years, alcohol consumption, DASH score, and physical activity.

[c]adjusted for all other variables.

Table 8. Estimated associations (risk ratios [RRs] and 95% confidence intervals [CIs]) between self-reported sleep duration and incident hypertension; overall model and stratified models by age, sex, ethnicity, and BMI.

		Hours of Sleep					
		≤5	**6**	**7**	**8**	**9**	**≥10**
	No. of events/No. of participants	3,198/7,961	9,489/23,848	12,231/32,934	9,201/22,734	2,290/6,130	641/1,660
		RR (95% CI)[a]					
Overall	37,050/97,267	1.00 (0.97-1.03)	1.04 (1.02-1.06)	1.00	1.00 (0.98-1.02)	1.00 (0.96-1.03)	0.98 (0.92-1.04)
Age							
45-54	14,045/38,205	1.05 (1.01-1.10)	1.05 (1.01-1.08)	1.00	1.01 (0.98-1.05)	1.08 (1.02-1.14)	1.03 (0.93-1.13)
55-64	13,196/32,268	0.98 (0.93-1.03)	1.03 (1.00-1.07)	1.00	1.00 (0.97-1.03)	0.98 (0.93-1.04)	0.98 (0.89-1.09)
≥65	9,809/26,794	0.94 (0.88-1.00)	1.02 (0.97-1.06)	1.00	0.98 (0.94-1.02)	0.92 (0.86-0.99)	0.95 (0.84-1.06)
Sex							
Male	15,344/42,301	1.00 (0.95-1.05)	1.05 (1.01-1.08)	1.00	0.98 (0.95-1.02)	1.00 (0.95-1.06)	1.02 (0.93-1.12)
Female	21,706/54,966	1.01 (0.97-1.04)	1.03 (1.00-1.06)	1.00	1.01 (0.99-1.04)	1.00 (0.96-1.05)	0.96 (0.88-1.04)
Ethnicity							
White	9,989/29,333	1.01 (0.94-1.09)	1.03 (0.99-1.08)	1.00	0.99 (0.95-1.02)	0.97 (0.91-1.03)	0.99 (0.87-1.12)
African American	5,004/10,457	1.00 (0.93-1.07)	1.06 (1.00-1.12)	1.00	1.05 (0.99-1.11)	1.04 (0.95-1.13)	1.00 (0.89-1.14)
Native Hawaiian	2,858/6,522	1.00 (0.92-1.09)	1.04 (0.97-1.11)	1.00	0.99 (0.92-1.07)	1.01 (0.90-1.14)	0.87 (0.70-1.08)
Japanese American	10,887/29,382	1.00 (0.94-1.06)	1.02 (0.98-1.06)	1.00	0.97 (0.93-1.01)	0.98 (0.91-1.06)	0.91 (0.77-1.07)
Latino	8,312/21,573	1.01 (0.95-1.08)	1.05 (1.01-1.10)	1.00	1.03 (0.98-1.07)	1.02 (0.95-1.09)	1.04 (0.93-1.15)
BMI (kg/m^2)							
Underweight	412/1,989	0.81 (0.57-1.14)	1.04 (0.84-1.31)	1.00	1.07 (0.85-1.34)	1.05 (0.71-1.55)	1.19 (0.68-2.08)
Normal	14,729/45,571	0.97 (0.92-1.03)	1.02 (0.99-1.06)	1.00	0.98 (0.95-1.02)	0.95 (0.89-1.01)	0.92 (0.81-1.04)
Overweight	14,744/35,701	1.04 (0.99-1.09)	1.04 (1.01-1.08)	1.00	1.01 (0.97-1.04)	1.00 (0.95-1.06)	1.05 (0.96-1.15)
Obese	7,165/14,006	0.99 (0.94-1.05)	1.05 (1.01-1.10)	1.00	1.02 (0.97-1.07)	1.07 (1.00-1.14)	0.96 (0.86-1.07)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, and DASH score.

Table 9. Estimated associations (risk differences [RDs] and 95% confidence intervals [CIs]) between self-reported sleep duration and prevalent hypertension on an additive scale; overall model and stratified models by age, sex, ethnicity, and BMI.

	Hours of Sleep					
	≤5	**6**	**7 (ref)**	**8**	**9**	**≥10**
			RD (95% CI)[a]			
Total Population						
Fully adjusted[b]	1 (-11, 13)	14 (6, 22)	0	-1 (-9, 7)	-3 (-16, 10)	-8 (-31, 16)
Age Group[c]						
45-54	27 (7, 46)	18 (6, 30)	0	5 (-8, 17)	27 (5, 48)	5 (-34, 44)
55-64	-11 (-31, 10)	11 (-3, 26)	0	0 (-14, 14)	-7 (-30, 16)	-2 (-44, 40)
≥65	-25 (47, -3)	8 (-8, 23)	0	-8 (-22, 8)	-27 (-50, -4)	-16 (-58, 25)
Sex[c]						
Male	0 (-19, 18)	18 (6, 30)	0	-6 (-18, 6)	1 (-18, 20)	10 (-24, 44)
Female	2 (-13, 17)	11 (0, 22)	0	5 (-6, 16)	-2 (-20, 15)	-19 (-51, 13)
Ethnicity[c]						
White			0			
African American	-7 (-38, 24)	24 (-2, 49)	0	17 (-10, 44)	9 (-34, 51)	-13 (-72, 46)
Native Hawaiian	4 (-36, 45)	17 (-14, 48)	0	-8 (-41, 26)	2 (-53, 57)	-66 (-150, 18)
Japanese American	-3 (-24, 19)	7 (-7, 20)	0	-10 (-25, 5)	-5 (-34, 23)	-32 (-88, 25)
Latino	5 (-19, 29)	19 (2, 37)	0	11 (-6, 28)	8 (-18, 34)	17 (-25, 59)
BMI[c]						
Underweight	-34 (-107, 40)	7 (-47, 60)	0	11 (-44, 66)	2 (-92, 96)	32 (-121, 184)
Normal	-6 (-24, 12)	8 (-4, 19)	0	-6 (-17, 5)	-14 (-33, 4)	-22 (-59, 15)
Overweight	17 (-3, 37)	19 (5, 32)	0	3 (-10, 17)	1 (-21, 23)	23 (-17, 62)
Obese	-4 (-33, 25)	25 (3, 48)	0	9 (-13, 32)	31 (-3, 66)	-24 (-76, 27)

[a]excess number of prevalent hypertension cases (per 1,000 individuals) associated with sleep categories compared to the referent 7-hour group.

[b]adjusted for age, sex, ethnicity, education level, BMI, smoking status, smoking pack-years, alcohol consumption, DASH score, and physical activity.

[c]adjusted for all other variables.

CHAPTER 3: ASSOCIATION BETWEEN SLEEP DURATION AND INCIDENT STROKE: THE MULTIETHNIC COHORT (MEC)

3.1 Introduction

Stroke, or cerebrovascular accident, is the sudden death of some brain cells due to the lack of oxygen when the blood flow to the brain is lost by blockage or rupture of an artery to the brain [136]. Strokes are the second leading cause of death worldwide, after ischemic heart disease [137]. According to estimates from the American Heart Association (AHA), the global prevalence of stroke in 2019 was 101.5 million people and strokes accounted for approximately 6.6 million deaths [138]. In 2018, the U.S. prevalence of stroke was estimated to be about 2.7%, affecting an estimated 7.6 million people [138]. Each year, approximately 610,000 people experience a new stroke and about 185,000 people have a recurrent episode [138].

There are two main types of strokes, and the first is ischemic stroke, which is caused by an interruption of the blood supply to a region in the brain, which results in a sudden loss of function. Hemorrhagic strokes are attributed to a rupture of a blood vessel or abnormal vascular structure [139]. Hemorrhagic strokes are further categorized into intracerebral hemorrhage and subarachnoid hemorrhage, where the former refers to bleeding within the brain, and the latter refers to bleeding between the brain and surrounding tissue.

3.1.1 Risk factors for stroke

There are many risk factors for stroke, which include age, sex, ethnicity, high blood pressure, smoking, obesity, diabetes, dyslipidemia, depression or psychosocial stress, physical

inactivity, poor nutrition, sleep duration and obstructive sleep apnea, and a family history of cardiovascular disease.

Stroke risk is known to increase with age, with the risk approximately doubling every decade after the age of 50 [140]. Stroke cases among women are higher, and according to the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), approximately 55,000 more women than men have a stroke annually in the U.S. [141]. In the Framingham Heart Study, the lifetime risk of stroke among elderly participants was found to be 1 in 5 for women and 1 in 6 in men [142]. There are also reports of disparities in stroke risk in different ethnic groups. In the Reason for Geographic and Racial Differences in Stroke (REGARDS) study, the age- and sex-adjusted incidence rate for stroke was higher among African American participants compared to white participants [143]. Trend data between years 2000 and 2010 in the U.S. also found increases in the incidence and mortality among African American adults, despite the overall decreasing trend of stroke incidence in this period [144]. There have also been previous reports of higher incidence of stroke in Mexican American people compared to non-Hispanic whites [145].

Hypertension is the number one modifiable risk factor for stroke. In the past two decades, there has been a strong correlation between the decreasing median systolic blood pressure and the decreasing incidence of stroke in the U.S. [146]. Numerous randomized controlled trials (RCTs) and meta-analyses have shown a decrease in stroke incidence in participants who maintained normal blood pressure [147]. In another meta-analysis of 11 studies, hypertension was associated with 67% increased odds of recurrent stroke [148]. Finally, it has been consistently shown that a systolic blood pressure of less than 130 mm Hg is the most clinically advantageous blood pressure target in the prevention of stroke [149, 150].

Diabetes is also a strong risk factor for stroke. In the GCNKSS conducted in 2005, middle-aged blacks and whites were 5.2 times and 12 times more likely to have a stroke episode, respectively, if they were diabetic [151]. This association also differ across sex, as one systematic review of 64 cohort studies found higher risk ratios among female participants [152].

Obesity is an important risk factor for stroke in both young adults and the elderly [153, 154], but whether this association is independent of other risk factors for stroke is debated [153]. In addition, there are still questions about the best measure of adiposity as it relates to cardiovascular disease risk. In the Cardiovascular Health Study consisting of elderly adults, BMI was a better predictor of incident stroke in men, whereas the waist-to-hip ratio (WHR) was a better predictor in women [154].

Current smoking is a strong risk factor of developing a stroke, and a recent meta-analysis of 141 cohort studies showed that even low cigarette consumption, such as 1-2 cigarettes per day, increases the risk of stroke [155]. There is also evidence, such as that from the REGARDS study, showing that secondhand smoke exposure also increases the risk of stroke by 30%, compared to those who do not smoke or have had secondhand exposure [156]. Finally, discontinuation of smoking has also been found to reduce stroke risk [157].

Physical inactivity is a significant risk factor for stroke, especially in middle-aged and elderly populations [158, 159]. For example, in the Northern Manhattan Study (NOMAS), the risk of incident stroke was 60% higher in inactive elderly participants, compared to active participants [160]. In the REGARDS study, participants who reported less than four physical activities per week were at a 20% increased risk of incident stroke compared to those exercising more than four sessions per week [161]. In the Atherosclerosis Risk in Communities (ARIC)

study, similar findings were found among both Caucasian and African American participants [162].

Dietary and nutritional interventions are one of the key components in stroke prevention and treatment. According to data from the 2009-2012 NHANES, the key dietary components associated with stroke incidence and deaths were low vegetable intake, low fruit intake, and high sodium intake [163]. In the international INTERSTROKE study involving 32 countries, participants with the healthiest diet, or the highest tertile in dietary quality score, were at 40% lower odds of having an incident stroke episode, compared to participants in the lowest tertile [164]. Results from RCTs have found that adherence to a Mediterranean-style diet was associated with a reduced risk of stroke [165].

Several observational studies and meta-analyses have found that depression or psychosocial stress is a risk factor for stroke. In a meta-analysis of 28 cohort studies with up to 29 years of follow-up, depression was associated with a 45%, 55%, and 25% increased risk of total, fatal, and ischemic stroke, respectively [166]. The INTERSTROKE study composed of middle-aged and elderly participants found 2.8 times greater odds of having a stroke in participants reporting psychological distress compared to control participants [164].

3.1.2 Sleep as a risk factor for stroke

In the past few decades, there has been increasing interest in the role of various sleep behaviors as it relates to the risk of developing cardiovascular disease, with majority of the research focusing on sleep quality and related disorders. Sleep apnea and sleep-disordered breathing are the most studied sleep risk factor for stroke, and they have been shown to be strongly associated with stroke and stroke mortality, independent of other risk factors and

comorbidities [167, 168]. Currently, treatment of sleep disorders is a common component of stroke rehabilitation, as better post-stroke outcomes, such as reducing the risk of recurrent strokes, have been reported in those with good sleep quality [46].

Compared to the known association between sleep disorders and stroke risk, the role of sleep duration is relatively understudied. Currently, reports examining this relationship have found that both sleep deprivation and excess sleep contribute to increased stroke risk. In the European Prospective Investigation into Cancer (EPIC) study conducted in Potsdam (1994-1998), short sleep duration (<6 hours/night) was found to increase the risk of incident stroke by 106%, compared to participants reporting 7-<8 hours of sleep per night [34]. In this study, there was also a 65% increased risk among participants reporting ≥9 hours of sleep. The EPIC study was also conducted in Norfolk in 1998-2009, and there was an 18% and 46% increased risk among those reporting <6 and ≥9 hours of sleep, respectively [35]. This finding where increased stroke risk was associated with both extremes of sleep duration, and where long sleep is attributed to higher increases in stroke risk, was reported in other studies [19, 36, 169-171].

The association between sleep duration and stroke is thought to be modified by other risk factors of stroke. In the previously mentioned EPIC-Norfolk study, the HRs for those reporting >8 hours of sleep were 1.46 and 1.80 among men and women, respectively [35]. Differences across sex were also reported in the Jichi Medical School Cohort study, in which short sleep was associated with a 100% increased risk of incident stroke in men, but no association was found in women [172]. There are other studies that have found no differences in the risk of stroke across sex, suggesting the need for more research on this topic [19, 36].

Race and ethnic background may also be potential modifiers of the sleep-stroke relationship. Based on the 2008-2010 REGARDS study, short sleep duration was significantly

associated with a decreased risk of stroke among black participants (HR: 0.49), particularly black men (HR: 0.21). Interestingly, no increases in stroke risk was seen among black participants who reported long sleep, although a 71% increased risk was observed within white males [173]. As with differences seen across sex, the role of ethnicity in the sleep-stroke relationship needs further research, especially in other ethnic groups in the U.S.

3.2 Objectives

The primary objective of this study was to estimate the association between self-reported sleep duration and incident stroke in the MEC study population. Based on existing reports, a J-shaped association was hypothesized, where both short and long sleep hours are associated with increased stroke risk, with stronger associations in those reporting long sleep, compared to short sleep. Second, this study also aimed to investigate this association in various strata of age, sex, ethnicity, BMI groups, history of hypertension, and history of diabetes.

The secondary objective of this study was to investigate the association between sleep duration and stroke by estimating risk differences, instead of risk ratios, between different sleep groups. This additional analysis allowed us to consider the risk of stroke using case numbers relative to the baseline stroke risk in participants reporting 7 hours of sleep.

3.3 Methods

3.3.1 Study Population

The description and recruitment strategy of the MEC was described in section 1.3. This study used data from questionnaire 1 (1993–1996), questionnaire 2 (1998–2002), questionnaire 3

(2003–2006), and questionnaire 4 (2008–2012). Participants were excluded from analysis if they were not part of the five main ethnic groups under study, had missing information on sleep duration, stroke status at baseline (Qx1), or height, weight, or smoking. Participants were also excluded if they reported a history of stroke at baseline or did not participate in any of the follow-up questionnaires. The final study sample to analyze the association between sleep duration and incident stroke was 152,622 participants (Figure 4).

3.3.2 Exposure Variable – Sleep duration

Information on sleep duration was obtained from the following question in the baseline MEC questionnaire: "On average, during the last year, how many hours in a day did you sleep (including naps)?". Participants were given six response categories: ≤5, 6, 7, 8, 9, or ≥10 hours and the reference group was defined as 7 hours of sleep to be consistent with many of the literature reviewed for this study. Hourly categorization of sleep was chosen as the primary analysis method to be consistent with previous literature [34, 170, 172, 173].

3.3.3 Outcome Variable – Incident Stroke

Stroke cases were identified based on the self-reported responses in the MEC questionnaires, based on the following question, "Has your doctor ever told you that you had any of the following? (Mark all that apply)". Incident stroke cases were defined as any stroke reported in Qx2, 3, and/or 4. Due to the nature of the question in the MEC questionnaire, it was not possible to distinguish new and recurrent cases. Participants who did not participate in any of the follow-up questionnaires would have unknown stroke status and were removed from the analytic sample. Participants who answered "Yes" in any of the follow-up questionnaires were

considered incident cases. Participants were considered a non-case if they never answered “Yes” and answered “No” in at least one of the follow-up questionnaires.

3.3.4 Potential Confounders

Potential confounders were selected *a priori* based on their known association with sleep duration and stroke. Briefly, a variable is a potential confounder if 1) it is associated with the exposure, 2) it is not an effect of the exposure as it relates to the disease, and 3) it is associated with and predictive of the disease, but not predicted by the disease [92]. The potential confounders considered were age at cohort entry (45-54, 55-64, ≥65 years), sex (male/female), ethnicity (White, African American, Native Hawaiian, Japanese American, and Latino), education level (≤12, 13–15, or ≥16 years), BMI (underweight <18.5 kg/m^2, normal weight 18.5–<25 kg/m^2, overweight 25–30 kg/m^2, and obese ≥30 kg/m^2), smoking status (never, past, or current smoker), smoking pack-years, alcohol consumption (below median and above or equal to median: men is <3.05 g/day and ≥3.05 g/day, women is 0 g/day and >0 g/day), caffeine (<100, 100–<200, ≥200 mg/day), physical activity (quartiles: 0.1-1.43, 1.44-4.40, 4.41-8.86, ≥8.87 MET-hours in men; 0.1-1.43, 1.44-2.86, 2.87-6.20, ≥6.21 MET-hours in women), DASH dietary score (quartiles; 8-21, 22-24, 25-27, ≥28), history of high blood pressure (yes/no) and history of diabetes (yes/no). Table 10 indicates the sections that describes the evidence of association of the potential confounder with the main study variables. All variables labeled section 3.3.4 are discussed in this section, otherwise, they were discussed in a previous section of this paper.

Table 10. List of literature showing evidence of the association between the potential confounders and sleep/stroke.

Variable	Sleep	Stroke
Age	Section 1.1.1 [4] Section 2.3.4 [93]	Section 3.1.1 [140]
Sex	Section 1.1.1 [4] Section 2.3.4 [94]	Section 3.1.1 [141, 142]
Ethnicity	Section 1.1.1 [4] Section 2.3.4 [29, 95, 96]	Section 3.1.1 [143-145]
Education Level	Section 2.3.4 [29, 97]	Section 3.3.4 [174-176]
BMI	Section 1.2 [16, 19-24, 99]	Section 3.1.1 [153, 154]
Smoking	Section 2.3.4 [79, 80]	Section 3.1.1 [155-157]
Alcohol consumption	Section 2.3.4 [100, 101]	Section 3.3.4 [177-179]
Caffeine consumption	Section 2.3.4 [102, 103]	Section 3.3.4 [180-182]
Dietary Quality (DASH)	Section 2.3.4 [105-107]	Section 3.1.1 [163-165]
Physical activity	Section 2.3.4 [109-112]	Section 3.1.1 [158-162]
History of Hypertension	Section 2.1.3 [31-33, 82]	Section 3.1.1 [146-148]
History of Diabetes	Section 1.2 [14, 17-19]	Section 3.1.1 [151]

There are reports showing that socioeconomic status is associated with stroke incidence, and it may be because it is one of many proxy measures of an individual's access to healthcare. In the Adherence Evaluation After Ischemic Stroke–Longitudinal (AVAIL) study, it was found that those with lower education and income were more likely to have an incident stroke episode and have worse post-stroke outcomes [174]. Also, trend data based on the Global Burden of Disease (GBD) study show that majority of stroke cases and stroke-related deaths occur in low- and middle-income countries [175]. In this study, education level was selected as a proxy variable to adjust for any confounding by socioeconomic status because many MEC participants did not report their income and job titles. In a previous report based on an Australian cohort, the age-standardized risk of stroke was inversely associated with education level [176].

Although there is a consensus that alcohol consumption increases the risk of stroke, the nature of the association is unclear. In the Nurses' Health Study, it was found that the RRs of stroke were 0.83 for those consuming <5 grams of alcohol/day, 0.79 for 5.0–14.9 grams/day,

0.87 for 15–29.9 grams/day, and 1.06 for 30 to 45 grams/day, compared to those reporting no alcohol consumption [177]. Several other studies have suggested that moderate drinking is protective against stroke [178, 179], although it is difficult to rule out other healthy behaviors associated with those who drink alcohol in moderation.

Studies investigating the association between caffeine consumption and the risk of stroke is sparse, but there is evidence that caffeine is used to reduce cerebral blood flow and maintain postural stability in stroke patients [180]. However, there are also studies that have found that caffeine-containing medicines were associated with a 123% increased odds of having a hemorrhagic stroke [181]. In a dose-response meta-analysis of 36 studies, a J-shaped association between coffee consumption and cardiovascular disease was found, with the lowest risk seen in those reporting 2–4 cups of coffee per day (Ding et al., 2014). Furthermore, caffeine consumption is known to increase vascular resistance, causing hypertension and cardiovascular disease [104, 183].

Based on the known associations between sleep duration, stroke, and confounding variables, Figure 5 shows the proposed causal diagram.

3.3.5 Statistical Analysis

Descriptive parameters of the population characteristics were shown as means and standard deviations for continuous variables and proportions for categorical variables. A one-way analysis of variance (ANOVA) was used to test differences in the means of baseline continuous variables across categories of sleep duration. For categorical variables, the χ^2 test was performed to compare distributions of baseline variables across categories of sleep duration.

Risk ratios (RRs) and 95% confidence intervals (CIs) for the association between incident stroke and sleep duration were estimated using a multivariable log-binomial model, with 7 hours of sleep as the reference group. The model was adjusted for all potential confounders (section 3.3.4). Stratified analyses by age, sex, ethnicity, BMI, hypertension status, and diabetes status, each adjusted for all variables except itself, were also presented. For secondary analysis, risk differences, as well as 95% CIs, were estimated to obtain the mean number of excess stroke cases associated with each sleep category (compared to the reference 7 hours).

Statistical significance was determined *a priori* as $p < 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Log-binomial models were conducted using the PROC GENMOD procedure in SAS, specifying 'binomial' as the distribution and 'log' as the link function to obtain ratio estimates. The 'identity' link function was used to estimate difference estimates.

3.4 Results

3.4.1 Demographics

During the study period between 1993 and 2012, 8,543 incident stroke cases were identified among 152,622 participants (Figure 4). The majority of participants reported 6-8 hours of sleep per day, with approximately 17.5% of the participants reporting ≤5, 9, or ≥10 hours of sleep (Table 11). The ethnic distribution in the study sample was 26.2% white, 14.3% African American, 7.3% Native Hawaiian, 31.0% Japanese American, and 21.2% Latino. The proportion of those reporting ≤5 hours was highest among African American participants (15.4%), followed by Native Hawaiian participants (13.3%). African American, Native Hawaiian, and Latino participants were more likely to report ≥10 hours of sleep, compared to white and Japanese

American participants. The proportion of those reporting 7 hours of sleep was highest in Japanese American (35.8%) and white (35.4%) participants, followed by Latinos (30.4%). White participants were the least likely to report short sleep (≤5 & 6 hours) and most likely to report 7 and 8 hours of sleep. Japanese American participants were the least likely to report long sleep (9 & ≥10 hours).

The proportion of participants reporting ≤5, 9 and ≥10 hours of sleep increased with age, while the likelihood decreased with increasing education level, caffeine, consumption, DASH dietary score, and physical activity score. The proportion of short sleepers were higher among female participants, while male participants were more likely to report normal and long sleep. Underweight participants were more likely to report extreme sleep, compared to participants in other BMI categories. Comparing participants in other BMI categories, the likelihood of reporting extreme sleep increased with BMI. Smoking pack-years increased with sleep duration. Participants reporting alcohol consumption less than the median level were more likely to report ≤5, 6, and ≥10 hours of sleep. Finally, participants were more likely to report ≤5, 9, and ≥10 hours of sleep if they had a history of hypertension or diabetes.

Participants with missing information in education level, alcohol consumption, caffeine consumption, DASH dietary score, and physical activity were more likely to report ≤5 and ≥10 hours of sleep, compared to those with valid information in these variables.

3.4.2 Incident stroke

There was a significant association between sleep duration and incident stroke in this study sample even after adjustment for covariates (Table 12). In the fully adjusted model, the risk of incident stroke was elevated among those reporting ≤5 (RR: 1.13, 95% CI: 1.05-1.21), 9 (RR: 1.09, 95% CI: 1.00-1.18), and ≥10 hours of sleep (RR: 1.39, 95% CI: 1.23-1.57).

Age-stratified analyses did not indicate any evidence of effect modification. Higher estimates were observed in participants aged 45-54 reporting ≤5 (RR: 1.32, 95% CI: 1.13-1.54), 9 (RR: 1.25, 95% CI: 1.03-1.52), and ≥10 hours (RR: 1.52, 95% CI: 1.16-1.99) of sleep, but the confidence intervals overlapped with estimates in the other two age groups. In sex-stratified analyses, the RRs among participants reporting ≤5 hours of sleep were 1.02 (95% CI: 0.90-1.14) and 1.21 (1.10-1.33), in men and women, respectively. There were no differences in estimates in all other sleep categories. Stratified analyses by ethnicity did not indicate any evidence of effect measure modification. However, among participants reporting ≥10 hours of sleep, higher estimates were observed among African American (RR: 1.57, 95% CI: 1.24-1.99), Native Hawaiian (RR: 1.51, 95% CI: 1.05-2.19), and Latino participants (RR: 1.56, 95% CI: 1.23-1.98), compared to White (RR: 1.07, 95% CI: 0.80-1.43) and Japanese American (RR: 1.21, 95% CI: 0.89-1.65) participants.

In this study sample, the association between sleep duration and incident stroke was stronger in underweight participants across all sleep categories. However, due to the small number of participants in this group, the confidence intervals were wide. Among participants reporting ≤5 hours of sleep, the RRs of incident stroke were 1.84 (95% CI: 0.98-3.44), 1.27 (95% CI: 1.12-1.44), 1.07 (95% CI: 0.95-1.21), and 1.02 (95% CI: 0.88-1.18), for underweight, normal BMI, overweight, and obese participants, respectively. Finally, stratified analysis by baseline hypertension and diabetes status revealed no effect measure modification by these factors.

Risk differences (RDs) were also computed to estimate the number of excess stroke cases theoretically associated with each sleep category, compared to 7 hours of sleep (Table 13). In the fully adjusted model, ≥10 hours of sleep were associated with 23 excess cases (per 1,000) of incident stroke. Stratified analyses by age groups did not show any evidence of effect measure

modification, although those reporting ≥10 hours of sleep, the number of excess cases was slightly higher in those aged ≥65 years (31 cases, 95% CI: 12-50), compared to those aged 45-54 (19 cases, 95% CI: -1-40) and 55-64 (17 cases, 95% CI: -1-34). Sex differences were only observed among those reporting ≤5 hours of sleep, with 2 (95% CI: -5-8) and 12 (95% CI: 6-18) excess stroke cases in men and women, respectively. Risk differences were also compared by ethnicity, BMI, hypertension status, diabetes status, but no differences were detected.

3.5 Discussion

In this study based on a large, ethnically diverse population, we report a significant association between sleep duration and incident stroke. Compared to participants reporting 7 hours of sleep per day, there was an elevated risk of stroke among participants reporting ≤5, 9, and ≥10 hours of sleep, and this association appeared to follow a U- or J-shaped curve as hypothesized. Our findings were consistent with previous studies, such as conclusions based on the two EPIC studies discussed in section 3.1.3 [34, 35]. Estimates obtained from our study was also similar to results from a meta-analysis of 18 studies, which found that both short and long sleep duration was associated with a 13% and 40% elevation in stroke risk, respectively [184]. Another meta-analysis that examined stroke risk by hourly increments found that compared to 7 hours of sleep, there was a 5% increase in stroke risk per 1-hour reduction and 18% increase per 1-hour elevation in sleep duration [36]. In the Women's Health Initiative study, a 14% and 70% increase in ischemic stroke risk was observed for women reporting ≤6 and ≥9 hours, respectively [170]. Interestingly, they also reported a 24% increase in stroke risk in participants reporting 8 hours of sleep, which we did not see in our study.

We believe that our findings are biologically plausible based on known mechanisms linking sleep with cardiovascular diseases. Currently, substantial evidence supports that the mechanism involves hypertension as a mediating factor in the pathway [185, 186]. In Chapter 2, it was discussed that poor sleep quality was associated with overactivity of the sympathetic nervous system [119], increased intima-media thickness of the artery [121], increased artery calcification [122], higher cortisol and cholesterol levels [123], decreased glucose tolerance [124], and increased production of proinflammatory cytokines [125]. However, the sleep-stroke relationship is probably more complex, as our study has found an association even after adjustment for hypertension status. In addition, there are many observational studies that found an independent association even after adjustment for blood pressure or hypertension status [35, 170, 172, 173]. This suggests that the association between sleep duration and stroke may be independent of hypertension or possibly differences in measurement error. While self-reported responses may be unreliable for ascertaining hypertension and stroke, it is likely that recall of acute events, like stroke, would be better than recall of chronic conditions, such as hypertension.

Our findings suggesting excess sleep as a stronger risk factor than sleep deprivation has been reported in previous reports (section 3.1.3). However, reasons for this observation are still unknown. We propose several hypotheses that may explain these findings. It is possible that the most likely reason for higher risk estimates in long sleepers is due to residual confounding by unmeasured medical conditions, socioeconomic status, and health statuses associated with long sleep. It is possible that long sleep is associated with a less healthy lifestyle, such as more time being sedentary. Long sleep may also represent underlying medical conditions, such as depression or psychosocial stress, which were either undiagnosed or unmeasured in previous studies, including ours. In comparison, although sleep deprivation is also a risk factor for stroke,

those reporting short sleep may have an overall healthier lifestyle. Shorter sleep also represents longer time being active, which may be the result of a healthier work and social life. Due to this complex relationship between sleep behaviors, cardiovascular disease, and subclinical disease, we cannot rule out the possibility of reverse causality bias, where the sleep behaviors we measured at baseline were a symptom, rather than a cause, of underlying cardiovascular disease. We do note, however, that there have been previous reports showing an association between sleep duration and stroke that remained even after adjustments for comorbidities and various measures of health status [35, 170].

Our study did not find strong evidence of effect measure modification by age, sex, ethnicity, BMI groups, hypertension status, or diabetes status. Small differences by age, sex, and BMI were observed among participants reporting extreme short and long sleep, but these differences were unlikely to be clinically relevant. We also found higher estimates in some strata that were expected to have a low risk of stroke, such as being 45-54 years of age or having normal BMI. We suspected that this finding was due to lower baseline risk associated with these groups, which would inflate ratio measure estimates. However, analysis of risk differences across age and BMI strata revealed that the number of excess stroke cases theoretically attributable to these sleep categories was also higher in younger participants and in those with normal BMI. Based on our literature review, there are a few reports that examined effect modification by sex and ethnicity with regards to the association between sleep duration and stroke. In the EPIC-Norfolk study, there was a 46% and 80% increase in stroke among male and female participants, respectively [35]. In the Jichi Medical School Cohort study, short sleep was associated with a 100% increased risk of incident stroke in men, but no association was found in women [172]. In comparison, findings from two previous meta-analyses found no sex

differences, much like findings from our study [19, 36]. The only previous study that examined ethnic differences of the sleep-stroke relationship was the 2008-2010 REGARDS study, in which short sleep duration increased stroke risk in white participants but not in African American participants [173]. Among long sleepers, no associations were observed among black participants, whereas long sleep was associated with a 71% increased risk of stroke among white males.

3.5.1 Strengths and Limitations

This study was based on a large ethnically diverse population with an extensive questionnaire, thereby allowing numerous confounding variables to be considered in the analysis. The large population size allowed for various stratified analysis, which was crucial as this study is one of the first to investigate the role of various stroke risk factors in modifying the sleep-stroke relationship. This study also took a unique approach in estimating the association using a combination of difference and ratio measures, which allowed us to consider the baseline risk associated with various levels of stroke risk factors to better understand relationships.

Our study also comes with several limitations. The first limitation is that information on sleep duration and covariates was self-reported at one point in time and that no objective measurements to validate the responses were available. In literature, findings on the validity of self-reported sleep measures compared to objective measures have been inconsistent. One report found that self-reported measures overestimates actual physiological sleep [133], whereas other studies concluded that subjective measurements are good estimates of objective sleep duration [134, 135]. Also, sleep duration obtained in this study was not specific to nocturnal sleep and reflect the number of hours over a 24-hour period, thus making our results difficult to compare with the previous literature. Findings from the 2011 China Health and Retirement Longitudinal

Study found a significant association between short sleep duration and the risk of stroke when the total sleep duration was considered, but no association was found when looking at daytime napping and nighttime sleep was considered alone [187].

Stroke status was also self-reported, and the validity of responses could not be confirmed. This may have introduced a selection bias, in which participants may have been erroneously classified to a stroke status, affecting our exclusion criteria. In the Australian Longitudinal Study of Women's Health, there was only a 0.35 and 0.56 agreement between self-reported stroke and hospital-recorded stroke among elderly and middle-aged women, respectively [188]. However, the questionnaire in this study also specified the type of stroke and stroke events within the past three years, which may have introduced a degree of difficulty for participants to accurately recall events. Another study that examined the validity of self-reported stroke in an ethnically diverse, elderly adult population found that the sensitivity and specificity, verified by an MRI, was 32.4% and 78.9%, respectively [189]. In addition, we were not able to distinguish between ischemic and hemorrhagic stroke, nor new and recurrent strokes.

All categorical variables in this study were subject to misclassification bias. However, it is unlikely that the misclassification of stroke status was related to sleep duration, and the misclassification, if any, would be a non-differential misclassification. This type of misclassification would bias the estimates of association toward the null, suggesting that the estimates reported in this report are conservative.

Finally, we are unable to rule out any residual confounding by unmeasured variables. Our study did not collect information on other sleep characteristics, such as sleep quality, sleep disorders, and use of sleep medications. Other suspected confounding variables include family

history of cardiovascular disease, history of depression or psychosocial stress, employment status, and job types.

3.6 Conclusion

This study found that both extreme short and long sleep were associated with higher risk of stroke in middle-aged and elderly adults in Hawai'i and L.A. Contrary to our hypothesis, this association was not found to differ by age, sex, ethnicity, BMI, hypertension status, and diabetes status. To date, there are very few reports that investigated the potential for these factors to modify the sleep-stroke relationship. Findings from this study backed up the current public health recommendation that 7 to 8 hours of sleep are associated with a lower risk of cardiovascular disease. However, the number of cases theoretically attributed to short or long sleep was small and the results may not appear to be clinically significant. This study also revealed the complexity in the sleep-stroke relationship, as it was discovered that there was an independent association regardless of hypertension status. This complexity warrants the need for future studies to focus on not just independent sleep factors, such as sleep duration, snoring, or insomnia, but to study sleep as a construct and develop new methods in characterizing sleep health.

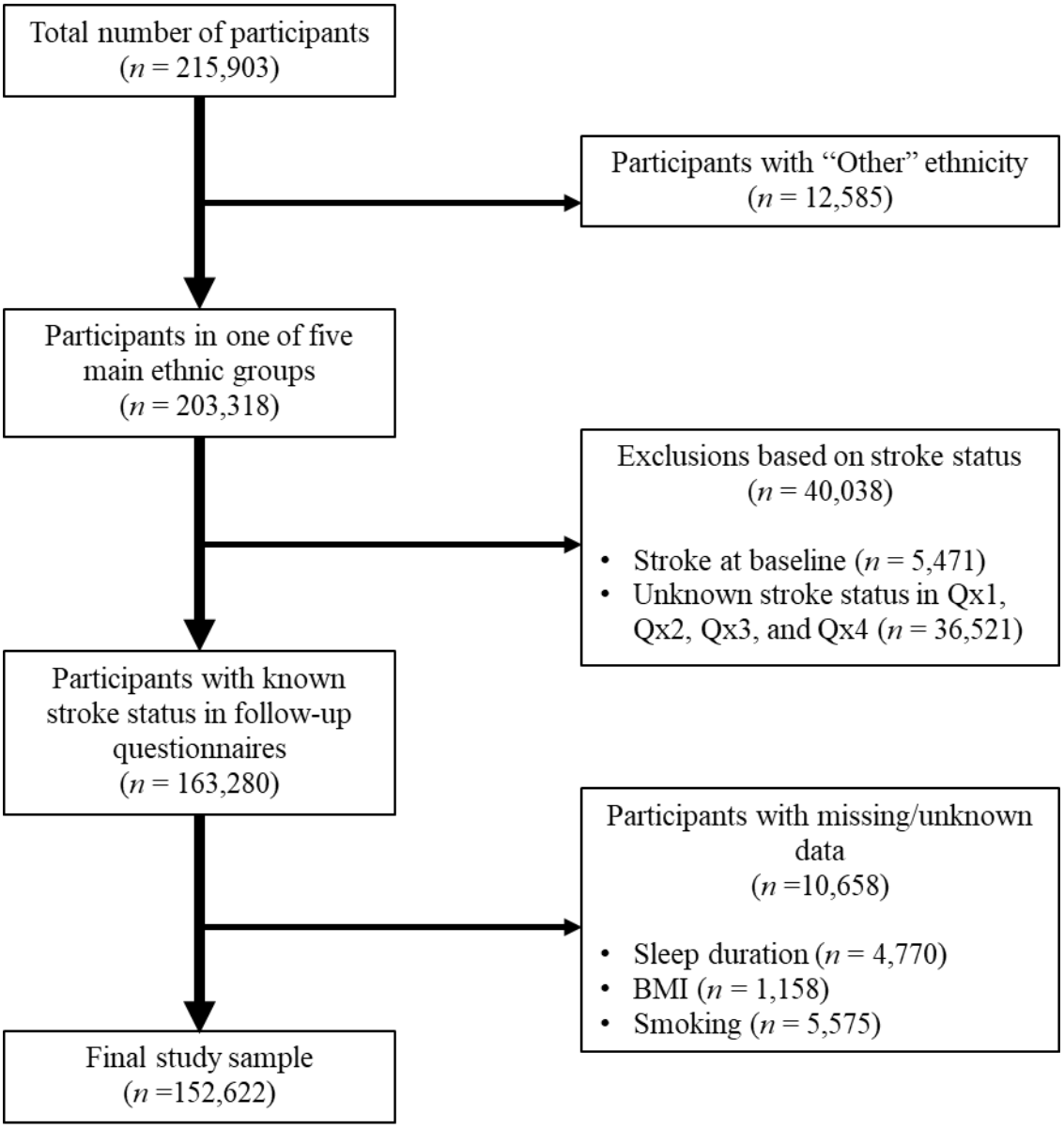

Figure 4. Exclusion criteria to analyze the association between sleep duration and incident stroke in the MEC, 1993–2012.

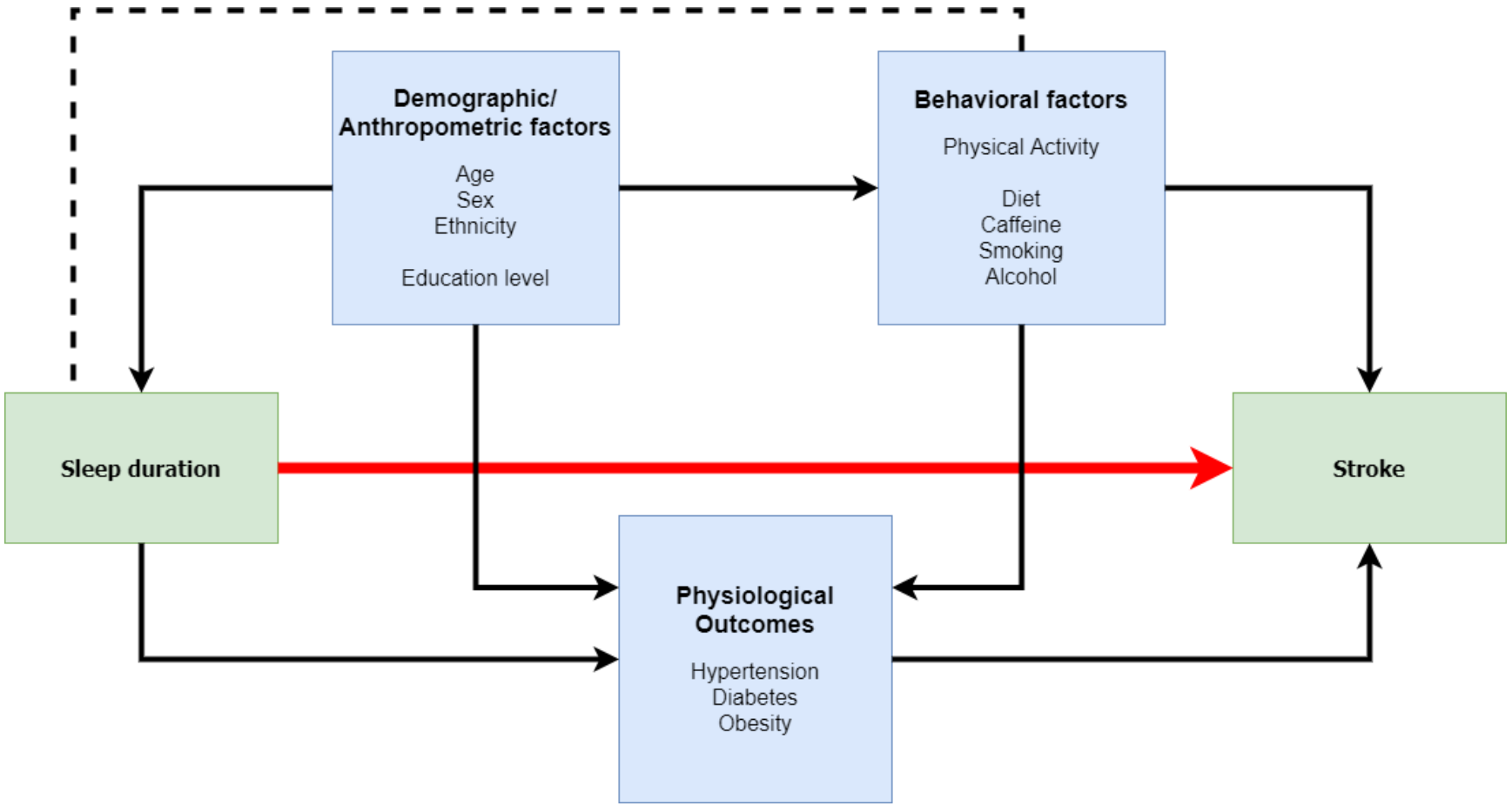

Figure 5. Causal diagram representing the relationship between sleep duration, stroke, and confounding variables. Dotted lines represent an association between factors and arrows represent causal direction.

Table 11. Demographic characteristics of participants at the baseline questionnaire (Aim 2), MEC, 1993-1996.

		Sleep Duration (Hours)						
	All (*n*)	**≤5**	**6**	**7**	**8**	**9**	**≥10**	***p*[c]**
Number of Participants	152,622	13,877 (9.1%)	37,918 (24.8%)	49,735 (32.6%)	38,254 (25.1%)	9,902 (6.5%)	2,936 (1.9%)	
Age (years)[a]								<0.0001
45-54	52,008	4,459 (8.5%)	13,812 (26.6%)	17,824 (34.3%)	12,136 (23.3%)	2,902 (5.6%)	875 (1.7%)	
55-64	51,769	4,762 (9.2%)	12,773 (24.7%)	16,928 (32.7%)	13,057 (25.2%)	3,270 (6.3%)	979 (1.9%)	
≥65	48,845	4,656 (9.5%)	11,333 (23.2%)	14,983 (30.7%)	13,061 (26.7%)	3,730 (7.7%)	1,082 (2.2%)	
Sex[a]								<0.0001
Male	67,702	5,396 (8.0%)	16,838 (24.9%)	22,333 (33.0%)	17,265 (25.5%)	4,490 (6.6%)	1,380 (2.0%)	
Female	84,920	8,481 (10.0%)	21,080 (24.8%)	27,402 (32.3%)	20,989 (24.7%)	5,412 (6.4%)	1,556 (1.8%)	
Ethnicity[a]								<0.0001
White	39,923	1,981 (5.0%)	7,635 (19.1%)	14,139 (35.4%)	12,252 (30.7%)	3,279 (8.2%)	637 (1.6%)	
African American	21,894	3,368 (15.4%)	5,781 (26.4%)	5,646 (25.8%)	4,975 (22.7%)	1,466 (6.7%)	658 (3.0%)	
Native Hawaiian	11,153	1,486 (13.3%)	3,112 (27.9%)	3,186 (28.6%)	2,419 (21.7%)	678 (6.1%)	272 (2.4%)	
Japanese American	47,329	3,903 (8.2%)	14,149 (29.9%)	16,930 (35.8%)	9,840 (20.8%)	2,023 (4.3%)	484 (1.0%)	
Latino	32,323	3,139 (9.7%)	7,241 (22.4%)	9,834 (30.4%)	8,768 (27.1%)	2,456 (7.6%)	885 (2.8%)	
Education[a]								<0.0001
≤12 years	61,731	7,044 (11.4%)	14,510 (23.5%)	18,119 (29.4%)	15,865 (25.7%)	4,517 (7.3%)	1,676 (2.7%)	
13-15 years	46,330	3,961 (8.5%)	12,045 (26.0%)	15,192 (32.8%)	11,386 (24.6%)	2,953 (6.4%)	793 (1.7%)	
≥16 years	44,049	2,799 (6.4%)	11,244 (25.5%)	16,287 (37.0%)	10,871 (24.7%)	2,400 (5.4%)	448 (1.0%)	
Missing	512	73 (14.3%)	119 (23.2%)	137 (26.8%)	132 (25.8%)	32 (6.2%)	19 (3.7%)	
BMI (kg/m^2)[a,c]								<0.0001
Underweight	2,473	246 (9.9%)	657 (26.6%)	792 (32.0%)	577 (23.3%)	150 (6.1%)	51 (2.1%)	
Normal	62,139	4,646 (7.5%)	15,243 (24.5%)	21,881 (35.2%)	15,695 (25.3%)	3,807 (6.1%)	867 (1.4%)	
Overweight	58,523	5,333 (9.1%)	14,761 (25.2%)	18,772 (32.1%)	14,763 (25.2%)	3,788 (6.5%)	1,106 (1.9%)	
Obese	29,487	3,652 (12.4%)	7,257 (24.6%)	8,290 (28.1%)	7,219 (24.5%)	2,157 (7.3%)	912 (3.1%)	
Smoking status[a]								<0.0001
Never	70,861	6,733 (9.5%)	17,926 (25.3%)	23,510 (33.2%)	17,343 (24.5%)	4,181 (5.9%)	1,168 (1.6%)	
Yes, quit	59,060	4,866 (8.2%)	14,291 (24.2%)	19,282 (32.7%)	15,328 (26.0%)	4,143 (7.0%)	1,150 (1.9%)	
Yes, current	22,701	2,278 (10.0%)	5,701 (25.1%)	6,943 (30.6%)	5,583 (24.6%)	1,578 (7.0%)	618 (2.7%)	

Smoking pack-years[b]	9.6 ± 14.5	8.7 ± 13.9	9.2 ± 14.1	9.3 ± 14.2	9.9 ± 14.7	11.3 ± 15.9	11.9 ± 16.5	
Alcohol consumption (g/day)[a]								<0.0001
<3.05 (men), 0 (women)	83,352	8,325 (10.0%)	21,618 (25.9%)	26,413 (31.7%)	20,239 (24.3%)	5,085 (6.1%)	1,672 (2.0%)	
≥3.05 (men), >0 (women)	64,249	4,793 (7.4%)	15,033 (23.4%)	22,017 (34.3%)	16,826 (26.2%)	4,492 (7.0%)	1,088 (1.7%)	
Missing	5,021	759 (15.1%)	1,267 (25.2%)	1,305 (26.0%)	1,189 (23.7%)	325 (6.5%)	176 (3.5%)	
Caffeine consumption (mg/day)[a]								<0.0001
<100	75,322	7,223 (9.6%)	18,604 (24.7%)	24,216 (32.2%)	18,943 (25.1%)	4,858 (6.4%)	1,478 (2.0%)	
100-<200	30,454	2,564 (8.4%)	7,329 (24.1%)	9,957 (32.7%)	7,934 (26.0%)	2,096 (6.9%)	574 (1.9%)	
≥200	41,825	3,331 (7.9%)	10,718 (25.6%)	14,257 (34.1%)	10,188 (24.4%)	2,623 (6.3%)	708 (1.7%)	
Missing	5,021	759 (15.1%)	1,267 (25.2%)	1,305 (26.0%)	1,189 (23.7%)	325 (6.5%)	176 (3.5%)	
DASH score[a]								<0.0001
8-21	41,889	4,287 (10.2%)	11,125 (26.6%)	13,246 (31.6%)	9,736 (23.3%)	2,609 (6.2%)	886 (2.1%)	
22-24	35,959	3,278 (9.1%)	9,001 (25.0%)	11,668 (32.5%)	8,982 (25.0%)	2,321 (6.4%)	709 (2.0%)	
25-27	35,404	3,002 (8.5%)	8,583 (24.2%)	11,759 (33.2%)	9,097 (25.7%)	2,359 (6.7%)	604 (1.7%)	
≥28	34,349	2,551 (7.4%)	7,942 (23.1%)	11,757 (34.2%)	9,250 (26.9%)	2,288 (6.7%)	561 (1.7%)	
Missing	5,021	759 (15.1%)	1,267 (25.2%)	1,305 (26.0%)	1,189 (23.7%)	325 (6.5%)	176 (3.5%)	
Physical activity (MET-hours/day)[a,d]								<0.0001
0.1-2.20 (men), 0.1-1.43 (women)	45,274	5,099 (11.3%)	11,390 (25.2%)	13,470 (29.7%)	11,082 (24.5%)	3,035 (6.7%)	1,198 (2.6%)	
2.21-4.77 (men), 1.44-3.00 (women)	31,069	2,779 (8.9%)	8,035 (25.9%)	10,216 (32.9%)	7,566 (24.4%)	1,962 (6.3%)	511 (1.6%)	
4.78-9.94 (men), 3.01-8.00 (women)	38,356	2,867 (7.5%)	9,498 (24.8%)	13,396 (34.9%)	9,600 (25.0%)	2,435 (6.3%)	560 (1.5%)	
≥9.95 (men), ≥8.01 (women)	32,038	2,417 (7.5%)	7,579 (23.7%)	10,919 (34.1%)	8,475 (26.5%)	2,122 (6.6%)	526 (1.6%)	
Missing	5,885	715 (12.1%)	1,416 (24.1%)	1,734 (29.5%)	1,531 (26.0%)	348 (5.9%)	141 (2.4%)	
History of Hypertension[a]								<0.0001
No	96,360	7,861 (8.2%)	23,650 (24.5%)	32,688 (33.9%)	24,486 (25.4%)	6,050 (6.3%)	1,625 (1.7%)	
Yes	56,262	6,016 (10.7%)	14,268 (25.4%)	17,047 (30.3%)	13,768 (24.5%)	3,852 (6.8%)	1,311 (2.3%)	
History of Diabetes[a]								<0.0001
No	137,656	12,097 (8.8%)	34,300 (24.9%)	45,523 (33.1%)	34,539 (25.1%)	8,796 (6.4%)	2,401 (1.7%)	
Yes	14,966	1,780 (11.9%)	3,618 (24.2%)	4,212 (28.1%)	3,715 (24.8%)	1,106 (7.4%)	535 (3.6%)	

[a]n (row %).
[b]mean ± SD.
[c]underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–30 kg/m^2), and obese (≥30 kg/m^2).

[d]METs for moderate and vigorous activity per day.
[e]p values calculated by analysis of variance and χ^2 test.

Table 12. Estimated associations (risk ratios [RRs] and 95% confidence intervals [CIs]) between self-reported sleep duration and incident stroke; overall model and stratified models by age, sex, ethnicity, BMI, history of hypertension, and history of diabetes.

		Hours of Sleep					
		≤5	**6**	**7**	**8**	**9**	**≥10**
	No. of events/No. of participants	895/13,877	2,069/37,918	2,568/49,735	2,131/38,254	622/9,902	258/2,936
		RR (95% CI)					
Overall[a]	8,543/152,622	1.13 (1.05-1.21)	1.03 (0.98-1.09)	1.00	1.02 (0.96-1.08)	1.09 (1.00-1.18)	1.39 (1.23-1.57)
Age Group[b]							
45-54	1,793/52,008	1.32 (1.13-1.54)	1.07 (0.95-1.21)	1.00	1.07 (0.94-1.22)	1.25 (1.03-1.52)	1.52 (1.16-1.99)
55-64	3,085/51,769	1.13 (1.00-1.28)	1.09 (0.99-1.19)	1.00	1.02 (0.93-1.12)	1.05 (0.91-1.22)	1.34 (1.08-1.65)
≥65	3,665/48,845	1.00 (0.89-1.12)	0.96 (0.88-1.04)	1.00	0.99 (0.91-1.07)	1.05 (0.93-1.18)	1.36 (1.14-1.63)
Sex[b]							
Male	4,111/67,702	1.02 (0.90-1.14)	1.02 (0.94-1.11)	1.00	1.02 (0.94-1.10)	1.06 (0.94-1.19)	1.35 (1.14-1.60)
Female	4,432/84,920	1.21 (1.10-1.33)	1.04 (0.96-1.13)	1.00	1.02 (0.94-1.10)	1.12 (0.99-1.26)	1.43 (1.20-1.70)
Ethnicity[b]							
White	2,197/39,923	1.10 (0.92-1.32)	1.04 (0.92-1.16)	1.00	1.02 (0.92-1.13)	1.12 (0.96-1.29)	1.07 (0.80-1.43)
African American	1,496/21,894	1.09 (0.93-1.28)	1.02 (0.89-1.17)	1.00	0.98 (0.85-1.13)	0.98 (0.79-1.22)	1.57 (1.24-1.99)
Native Hawaiian	657/11,153	1.03 (0.81-1.30)	0.93 (0.76-1.14)	1.00	1.00 (0.81-1.24)	1.25 (0.94-1.68)	1.51 (1.05-2.19)
Japanese American	2,559/47,329	1.16 (1.02-1.33)	0.99 (0.90-1.09)	1.00	0.96 (0.87-1.07)	1.00 (0.83-1.20)	1.21 (0.89-1.65)
Latino	1,634/32,323	1.16 (0.98-1.38)	1.18 (1.03-1.35)	1.00	1.13 (0.99-1.28)	1.15 (0.95-1.38)	1.56 (1.23-1.98)
BMI (kg/m^2)[b]							
Underweight	114/2,473	1.84 (0.98-3.44)	1.42 (0.85-2.37)	1.00	1.50 (0.89-2.53)	1.87 (0.88-3.96)	1.91 (0.68-5.37)
Normal	3,048/62,139	1.27 (1.12-1.44)	1.08 (0.98-1.18)	1.00	1.01 (0.92-1.10)	1.04 (0.90-1.21)	1.30 (1.02-1.66)
Overweight	3,401/58,523	1.07 (0.95-1.21)	1.00 (0.92-1.10)	1.00	1.02 (0.94-1.11)	1.04 (0.91-1.19)	1.37 (1.12-1.67)
Obese	1,980/29,487	1.02 (0.88-1.18)	0.99 (0.87-1.11)	1.00	1.00 (0.89-1.13)	1.19 (1.01-1.40)	1.44 (1.17-1.77)
History of Hypertension[b]							
No	4,087/96,360	1.17 (1.05-1.31)	1.03 (0.95-1.12)	1.00	1.03 (0.95-1.11)	1.11 (0.98-1.26)	1.42 (1.17-1.72)
Yes	4,456/56,262	1.09 (0.98-1.20)	1.03 (0.95-1.11)	1.00	1.01 (0.94-1.09)	1.07 (0.96-1.20)	1.37 (1.17-1.60)
History of Diabetes[b]							

No	7,045/137,656	1.12 (1.03-1.22)	1.05 (0.99-1.12)	1.00	1.05 (0.99-1.11)	1.08 (0.98-1.19)	1.42 (1.23-1.64)
Yes	1,498/14,966	1.11 (0.94-1.30)	0.92 (0.80-1.05)	1.00	0.89 (0.77-1.02)	1.10 (0.91-1.33)	1.28 (1.01-1.61)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, history of hypertension, and history of diabetes.
[b]adjusted for all other variables.

Table 13. Estimated associations (risk differences [RDs] and 95% confidence intervals [CIs]) between self-reported sleep duration and incident stroke; overall model and stratified models by age, sex, ethnicity, BMI, history of hypertension, and history of diabetes.

	Hours of Sleep					
	≤5	**6**	**7 (ref)**	**8**	**9**	**≥10**
			RD (95% CI)[a]			
Total Population						
Fully adjusted[b]	8 (3, 13)	2 (-1, 5)	0	2 (-1, 6)	6 (0, 11)	23 (12, 35)
Age Group[c]						
45-54	12 (3, 21)	2 (-4, 8)	0	3 (-3, 8)	9 (-2, 19)	19 (-1, 40)
55-64	7 (0, 15)	6 (1, 11)	0	3 (-2, 8)	3 (-6, 11)	17 (-1, 34)
≥65	0 (-9, 9)	-3 (-9, 4)	0	-1 (-7, 5)	2 (-7, 12)	31 (12, 50)
Sex[c]						
Male	2 (-5, 8)	2 (-2, 6)	0	2 (-2, 6)	3 (-4, 11)	30 (10, 40)
Female	12 (6, 18)	2 (-2, 6)	0	2 (-2, 6)	7 (0, 14)	22 (8, 36)
Ethnicity[c]						
White	6 (-5, 17)	1 (-5, 7)	0	1 (-4, 6)	8 (-1, 16)	5 (-14, 24)
African American	4 (-1, 15)	-1 (-10, 7)	0	3 (-6, 11)	-2 (-15, 11)	38 (14, 62)
Native Hawaiian	1 (-23, 24)	-4 (-22, 14)	0	0 (-20, 19)	14 (-16, 45)	34 (-14, 81)
Japanese American	13 (5, 21)	1 (-3, 5)	0	0 (-5, 5)	1 (-8, 11)	11 (-13, 35)
Latino	5 (-7, 18)	8 (-1, 17)	0	6 (-2, 15)	7 (-6, 20)	26 (3, 48)
BMI[c]						
Underweight	23 (-36, 81)	13 (-28, 54)	0	16 (-27, 60)	27 (-40, 94)	33 (-81, 146)
Normal	14 (6, 22)	3 (-1, 8)	0	1 (-3, 5)	4 (-3, 11)	18 (1, 35)
Overweight	5 (-5, 14)	0 (-6, 7)	0	2 (-4, 9)	2 (-9, 13)	21 (1, 42)
Obese	2 (-10, 13)	2 (-7, 10)	0	1 (-8, 10)	13 (-1, 28)	31 (8, 54)
History of Hypertension[c]						
No	8 (1, 14)	2 (-2, 6)	0	2 (-2, 6)	5 (-2, 12)	18 (4, 32)
Yes	9 (1, 17)	4 (-2, 10)	0	2 (-4, 8)	6 (-3, 15)	34 (16, 51)
History of Diabetes[c]						
No	7 (2, 13)	3 (-1, 6)	0	3 (-1, 7)	5 (-1, 11)	22 (10, 34)
Yes	16 (-2, 33)	-8 (-20, 5)	0	-8 (-21, 4)	11 (-10, 31)	31 (1, 61)

[a]excess number of incident stroke cases (per 1,000 individuals) associated with sleep categories compared to the referent 7-hour group.
[b]adjusted for age, sex, ethnicity, education, smoking status, BMI, smoking pack-years, alcohol consumption, DASH score, physical activity, history of hypertension, and history of diabetes.
[c]adjusted for all other variables.

CHAPTER 4: ASSOCIATION BETWEEN SLEEP DURATION, ALL-CAUSE, CARDIOVASULCAR, AND STROKE MORTALITY IN THE MULTIETHNIC COHORT (MEC)

4.1 Introduction

In the past 20 years, sleep habits and patterns, particularly sleep duration, have been gaining attention as important modifiable risk factors for early mortality. There have been numerous reports suggesting that sleep duration shorter or longer than the recommended 7 to 8 hours of sleep per night has been associated with a higher risk of all-cause, cardiovascular, stroke, and cancer mortality [29, 40, 41, 190-204]. In the National Institutes of Health (NIH)-AARP Diet and Health Study, extreme short (<5 hours) and long sleep (≥9 hours) was found to increase the risk of death by 16% and 11%, respectively [40]. Similarly, a 25% increase in cardiovascular mortality risk was seen among short sleepers [40]. In a previous MEC study, the hazard ratios (HRs) of all-cause mortality, with 7 hours as the reference, were 1.15 (95% CI: 1.06-1.23), 1.04 (0.99-1.10), 1.07 (1.01-1.12), and 1.19 (1.12-1.17), for those reporting ≤5, 6, 8 and ≥9 hours of sleep, respectively [29]. This study also found similar associations for cardiovascular and stroke mortality [29]. Although this U- or J-shaped association between sleep duration and mortality is found commonly in reports, there are also a few studies that have only found an association only among short or long sleep [196, 205, 206].

Although findings have been inconsistent, the association between sleep duration and mortality is also believed to differ by various factors such as age [200, 207], sex [41, 196, 207, 208], ethnicity [29], and BMI [29, 40, 207]. In the Asia Cohort Consortium (1984-2002) study compiling results from nine prospective studies in Asia, the risk of all-cause and cardiovascular

mortality among male participants was found to be higher in the younger age group (<65 years), compared to the older group (≥65 years), while no differences by age was observed in females [207]. The investigators also noted that among male participants, the risk of mortality was higher in those with lower BMI (<25 kg/m^2). Sex differences in the risk of mortality was observed in the Shizuoka study of elderly participants, where men reporting over 10 hours of sleep was at an 86% increased risk of all-cause mortality, while women in the same sleep category experienced a 127% increased risk [208]. Ethnic differences of the sleep-mortality relationship was examined in a previous MEC report, and while there appeared to be small differences across ethnicity, the authors concluded that there were no differences [29].

4.2 Objectives

The primary objective of this study was to estimate the association between self-reported sleep duration and mortality in the MEC study population. Consistent with previous findings, it was expected for both short and long sleepers to be at increased risk of mortality, compared to those reporting recommended sleep hours. In addition, this study aimed to investigate differences in this association by age, sex, ethnicity, BMI, hypertension status, and diabetes status. Joint associations of sleep duration and BMI were examined by comparing various sleep-BMI combinations to those reporting 7 hours of sleep and having normal BMI. It was hypothesized that combinations of obesity with short and long sleep would be associated with increased risk of mortality. Joint associations of sleep duration and hypertension and diabetes were also examined.

The secondary objective of this study was to conduct an analysis specific to cardiovascular and stroke mortality. Stratified and joint analyses were also conducted for these outcomes.

4.3 Methods

4.3.1 Study Population

The description and recruitment strategy of the MEC was described in section 1.3. This study used population characteristics data from questionnaire 1 (1993–1996). Participants were excluded from analysis if they were not part of the five main ethnic groups under study or were missing information on sleep duration, height or weight, or smoking pack-years. Finally, participants were excluded if they reported a history of stroke or cancer at baseline. The final study sample to analyze the association between sleep duration and prevalent hypertension was 128,629 participants (Figure 6).

4.3.2 Exposure variable – Sleep duration

Information on sleep duration was obtained from the following question in the baseline MEC questionnaire: "On average, during the last year, how many hours in a day did you sleep (including naps)?". Participants were given six response categories: ≤5, 6, 7, 8, 9, or ≥10 hours and the reference group was 7 hours of sleep to be consistent with many of the literature reviewed for this study. Hourly categorization of sleep was chosen as the primary analysis method as it was more common in previous literature [40, 191, 195, 196, 200, 203, 206, 207].

4.3.3 Outcome variable – Mortality

Identification of the survival status and cause of death were obtained by record linkage of the MEC database with Vital Records in Hawaii and California (Kolonel et al., 2000) until 2016. Causes of death were coded according to the International Classification of Disease, Ninth

Revision (ICD-9) and Tenth Revision (ICD-10). The ICD codes for cardiovascular disease and stroke are shown on Table 14.

Table 14. ICD-9 and ICD-10 coding assignments and the number of death cases for cause-specific mortality among 128,629 participants in the MEC, 1993-2016.

	ICD Code		Death	
Cause of death	ICD-9	ICD-10	Cases	Proportion (%)
All-cause			53,052	
Cardiovascular disease			24,965	47.1
Coronary Heart Disease[a]	410-414, 429	I20-I25	12,063	22.7
Stroke	430-438	I60-I69	4,856	9.2
Cardiomyopathy	425	I42	865	1.6
Cardiac Arrest	427	I46	751	1.4
Hypertensive Heart Disease	402-404	I11-13	1,367	2.6
Hypertension	401-405	I10, I12	759	1.4
Congestive Heart Failure	428	I50	1,599	3.0
Aortic Aneurysm	441	I71	362	0.7
All other major CVD	394-398, 410-429, 440-447	I05-I09, I26-I28, I30-I52, I70-I79	2,343	4.4

[a]myocardial infarction and ischemic heart disease

4.3.4 Potential confounders

Potential confounders were selected *a priori* based on their known association with sleep duration and mortality. Briefly, a variable is a potential confounder if 1) it is associated with the exposure, 2) it is not an effect of the exposure as it relates to the disease, and 3) it is associated with and predictive of the disease, but not predicted by the disease [92]. The potential confounders considered were age at cohort entry (45-54, 55-64, ≥65 years), sex (male/female), ethnicity (White, African American, Native Hawaiian, Japanese American, and Latino), education level (≤12, 13–15, ≥16 years, missing), marital status (married, not married, missing), BMI (underweight <18.5 kg/m^2, normal weight 18.5–<25 kg/m^2, overweight 25–30 kg/m^2, and

obese ≥30 kg/m^2), smoking status (never, past, current smoker, missing), smoking pack-years, alcohol consumption (below median and above or equal to median: men is <2.32 g/day and ≥2.32 g/day, women is 0 g/day and >0 g/day), caffeine consumption (<100, 100–<200, ≥200 mg/day), physical activity (quartiles: 0.1-1.97, 1.98-4.77, 4.78-8.86, ≥8.87 MET-hours in men; 0.1-1.43, 1.44-2.86, 2.87-6.40, ≥6.41 MET-hours in women), DASH dietary score (quartiles; 8-21, 22-24, 25-27, ≥28), history of high blood pressure (yes/no) and history of diabetes (yes/no).

Table 15 shows the sections in this dissertation that describes the evidence of association of the potential confounder with the main study variables. All variables labeled with section 4.3.4 are discussed in this section, otherwise, it was discussed in a previous section in this dissertation.

Table 15. List of literature showing evidence of the association between the potential confounders and sleep/mortality.

Variable	Sleep	Mortality
Age	Section 1.1.1 [4] Section 2.3.4 [93]	Section 4.3.4 [55]
Sex	Section 1.1.1 [4] Section 2.3.4 [94]	Section 4.3.4 [55]
Ethnicity	Section 1.1.1 [4] Section 2.3.4 [29, 95, 96]	Section 4.3.4 [54]
Education Level	Section 2.3.4 [29, 97]	Section 4.3.4 [209]
Marital status	Section 4.3.4 [210, 211]	Section 4.3.4 [212, 213]
BMI	Section 1.2 [16, 19-24, 99]	Section 4.3.4 [214]
Smoking	Section 2.3.4 [79, 80]	Section 4.3.4 [214]
Alcohol consumption	Section 2.3.4 [100, 101]	Section 4.3.4 [214]
Caffeine consumption	Section 2.3.4 [102, 103]	Section 4.3.4 [215, 216]
Dietary Score (DASH)	Section 2.3.4 [105-107]	Section 4.3.4 [217, 218]
Physical activity	Section 2.3.4 [109-112]	Section 4.3.4 [214, 219, 220]
History of Hypertension	Section 2.1.3 [31-33, 82]	Section 4.3.4 [214]
History of Diabetes	Section 1.2 [14, 17-19]	Section 4.3.4 [214]

Although the global average life expectancy has been increasing over the years, age is still one of the most important risk factors for mortality [55]. Mortality risk is also known to differ by sex. According to the 2017 National Vital Statistics Reports, the age-adjusted death rate for males was 1.4 times that of females [55]. Significant differences in death rates are also seen across different ethnic groups. According to the CDC, the age-adjusted death rates (per 100,000) in 2019 were 561.2, 383.5, 843.6, and 717.3 for American Indian/Alaska Native, Asian/Pacific Islander, Black/African American, and White individuals, respectively [54].

Education level was used as a proxy measure for an individual's socioeconomic status. In a previous Chinese study, education level was found to be inversely associated with the risk of mortality [209]. Marital status was also a potential confounder in this study, and in general, being married was protective against mortality risk, compared to being single or divorced [212, 213]. The exact nature of the relationship between marital status and sleep is inconsistent [210, 211], and there are also reports suggesting that the quality of the marriage and its associated happiness may confound this association [221].

Obesity is a well-established risk factor for mortality and in 2017, obesity was ranked the 5th leading risk factor for death, accounting for approximately 4.7 million deaths globally [214]. In this study, BMI categories were defined as normal weight (<25 kg/m^2), overweight (25–30 kg/m^2), and obese (≥30 kg/m^2) based on the CDC definitions [222]. Due to the small number of underweight participants (<18.5-25 kg/m^2), this group was combined with the normal BMI group. Related to the BMI-mortality relationship, the lack of physical activity is also a risk factor for mortality [214]. In an interventional study conducted in England, participation in at least three sessions of moderate-to-vigorous physical activity (MVPA) per week was associated with a 39% decreased risk of death due to cardiovascular disease [220]. A similar association was seen in the

NHIS study, in which participants who adhered to the 2008 Adult Physical Activity Guidelines had a 35% reduction in risk of overall death [219]. In this study, physical activity was measured using metabolic equivalent of tasks (METs) of MVPA per week. Briefly, the MET is a ratio measure of the energy cost associated with the activity in comparison to the resting metabolic rate (sitting quietly). Compared to one MET, equivalent to sitting still, a brisk walk, bicycling, and jogging have scores of 3, 5.5, and 7, respectively. In this study, MET-hours of MVPA per day was divided into sex-specific quartiles for analysis.

Smoking and alcohol use are two behavioral risk factors that significantly contribute to the incidence of various diseases and mortality. In 2017, smoking was the second highest risk factor attributed to death, accounting for approximately 7.1 million deaths globally [214]. In that same year, alcohol use accounted for approximately 2.8 million deaths [214]. Smoking status in this study was measured using the following categories: never smoker, past smoker, and current smoker. To minimize residual confounding, smoking pack-years was also introduced to the model. Alcohol consumption was categorized based on sex-specific medians.

Previous reports suggested an inverse relationship between caffeine consumption and mortality. In a 10-year review of the NHANES data, compared to those who did not consume coffee, there was a 43%, 50%, and 61% decrease in the risk for mortality among women who consumed <100 mg, 100–<200 mg, and ≥200 mg of caffeine per day, respectively [215]. Interestingly, caffeine consumption was not associated with mortality in men. In another study with similar design and caffeine categories, participants consuming 100-<200 mg/day and ≥200 mg were found to have the lowest risk of mortality [216]. Caffeine consumption was categorized into the following categories: <100 mg, 100–<200 mg, and ≥200 mg.

In this study, adherence to the DASH diet was used as a measure of diet quality to be consistent with Chapters 2 and 3. Adherence to the DASH diet is known to be protective against mortality. In the EPIC-Norfolk study, compared to those with the least adherence to the DASH diet, there were incremental protective effects against total and CVD mortality in all groups that had higher adherence scores [218]. Similar incremental protective effects of the DASH diet were also seen in the Women's Health Initiative participants [217].

Finally, the models in this study were also adjusted for baseline histories of high blood pressure and diabetes for their known association with sleep duration and mortality [214].

Based on the known associations between sleep duration, mortality, and confounding variables, the following causal diagram was proposed (Figure 7).

4.3.5 Statistical analysis

Descriptive parameters of the population characteristics were shown as means and standard deviations for continuous variables and proportions for categorical variables. A one-way analysis of variance (ANOVA) was used to test differences in the means of baseline continuous variables across categories of sleep duration. For categorical variables, the χ^2 test was performed to compare distributions of baseline variables across categories of sleep duration.

Person-years for each subject were calculated by taking the difference between the date of cohort entry and the date of death or the end of the study (December 31, 2016), whichever occurred first. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, cardiovascular, and stroke mortality in association to sleep duration were estimated using Cox's proportional hazards model with age as the time metric and 7 hours of sleep as the reference category.

The overall model was adjusted for all potential confounders. Effect measure modification was evaluated by performing analyses stratified by age, sex, ethnicity, BMI, hypertension status, and diabetes status. To evaluate the synergistic effect of sleep duration and BMI, combined categories for six sleep categories and three BMI categories were created and estimates were obtained setting participants with 7 hours of sleep and normal BMI as the reference group. Joint associations of sleep duration with hypertension and diabetes on the risk of mortality was investigated by setting participants reporting 7 hours of sleep and no history of hypertension or diabetes as the reference group.

A sensitivity analysis was conducted by excluding death cases occurring in the first 3 years after cohort entry. Statistical significance was determined *a priori* as $p < 0.05$. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC), using the 'PHREG' procedure to run the Cox's proportional hazards model.

4.4 Results

4.4.1 Demographics

The majority of participants (82%) reported 6-8 hours of sleep per day (Table 16). The ethnic distribution in the study sample was 25.6% white, 14.8% African American, 7.1% Native Hawaiian, 29.5% Japanese American, and 23.0% Latino. African American participants were more likely to report ≤5 hours (16.1%), while white participants were the least likely (5.4%). African American participants were also more likely to report ≥10 hours (3.6%) of sleep, while Japanese American (1.1%) and white (1.8%) participants were the least likely. White participants were more likely to report 7 and 8 hours of sleep, while African American and Native Hawaiian participants were the least likely.

The likelihood of reporting extreme sleep (≤5 and ≥ 10 hours) increased with age and BMI, and decreased with education level, alcohol and caffeine consumption, dietary score, and physical activity (Table 16). The proportion of participants in each sleep category was similar across sex. Compared to participants who were married, those who were not married at the baseline questionnaire were more likely to report extreme short sleep. Consumption of cigarettes increased with sleep duration, and this was consistent with higher proportions of current smokers, compared to never and past smokers, in the 9 and ≥10-hour sleep groups. Participants with a history of hypertension or diabetes were more likely to report extreme sleep compared to those who did not report these conditions.

4.4.2 Total Mortality

During a mean of 19.9 years of follow-up, 53,052 deaths occurred among the final study sample of 128,629 participants. The association between sleep duration and all-cause mortality was J-shaped, and an increased mortality risk was observed among participants reporting ≤5 (HR: 1.12, 95% CI: 1.09-1.16), 9 (HR: 1.13, 95% CI: 1.09-1.17), and ≥10 hours of sleep (HR: 1.39, 95% CI: 1.32-1.46) (Table 17). Stratified analyses by age indicated higher HRs among participants aged 45-54 years, compared to those aged 55-64 or ≥65 years, in the ≤5 (HR: 1.25, 95% CI: 1.16-1.36), 9 (HR: 1.29, 95% CI: 1.17-1.43), and 10-hour (HR: 1.55, 95% CI: 1.35-1.77) sleep groups (Table 17). There were small differences in the ethnic-specific analyses, although no clear patterns were observed. Among participants reporting ≥10 hours of sleep, Japanese Americans had a much higher HR (HR: 1.68, 95% CI: 1.48-1.90) compared to other ethnic groups. BMI-specific analyses indicated that among participants reporting ≤5 hours of sleep, mortality risk was higher in those with normal BMI (HR: 1.22, 95% CI: 1.16-1.28), compared to those who were overweight (HR: 1.09, 95% CI: 1.03-1.14) or obese (HR: 1.08, 95%

CI: 1.02-1.15). Among participants reporting ≥10 hours, mortality risk was lower in obese participants (HR: 1.28, 95% CI: 1.17-1.40) compared to participants with normal BMI (HR: 1.46, 95% CI: 1.33-1.60), were underweight (HR: 1.51, 95% CI: 1.11-2.06) or were overweight (HR: 1.39, 95% CI: 1.28-1.52). Differences by sex, hypertension status, and diabetes status were not observed.

4.4.3 Cardiovascular and stroke mortality

There were 24,965 deaths due to cardiovascular disease in this study. There was a J-shaped association between sleep duration and cardiovascular mortality, with increased risk among participants reporting ≤5 (HR: 1.14, 95% CI: 1.10-1.20), 9 (HR: 1.13, 95% CI: 1.08-1.19), and ≥10 hours of sleep (HR: 1.42, 95% CI: 1.32-1.53) (Table 18). Results from stratified analyses revealed similar trends to that of total mortality, where small differences by age, ethnicity and BMI were observed. In an age-stratified analysis, participants aged 45-54 years was at a 33% increased risk (95% CI: 1.18-1.50) of cardiovascular mortality if they reported ≤5 hours of sleep, whereas only a 10% increase in mortality risk was observed among participants aged 55-64 and ≥65 years. In those reporting ≥10 hours of sleep, the HRs for those aged 45-54, 55-64, and ≥65 years were 1.72 (95% CI: 1.42-2.09), 1.31 (95% CI: 1.15-1.50), and 1.39 (95% CI: 1.26-1.53), respectively.

There were 4,856 deaths due to stroke in this study. The elevated risk of stroke mortality associated with ≥10 hours of sleep was higher (HR: 1.53, 95% CI: 1.30-1.81) compared to all-cause (HR: 1.39, 95% CI: 1.32-1.46) or cardiovascular mortality (HR: 1.42, 95% CI: 1.32-1.53) (Table 19). Stratified analyses did not reveal any differences across different levels of age, sex, ethnicity, BMI, hypertension status, or diabetes status.

4.4.4 Sensitivity Analysis

In a sensitivity analysis that excluded deaths occurring in the first 3 years from cohort entry, the association between sleep duration and all-cause, cardiovascular, and stroke mortality did not change (Table 20).

4.4.5 Joint association of sleep and BMI, hypertension, and diabetes

In an analysis that examined the combined association of sleep duration and BMI, the highest mortality risk was associated with underweight participants reporting ≥10 hours of sleep (HR: 2.97, 95% CI: 2.25-3.91) (Table 21). Estimates among those underweight were consistently higher than other BMI groups in corresponding sleep categories. Combinations of being obese and reporting ≤5 (HR: 1.34, 95% CI: 1.27-1.42), 9 (HR: 1.38, 95% CI: 1.29-1.47), or ≥10 hours (HR: 1.59, 95% CI: 1.45-1.73) of sleep was also associated with elevated risk of mortality. Similar synergistic associations were observed for cardiovascular and stroke mortality.

Compared to participants reporting 7 hours of sleep and without a history of hypertension at baseline, those reporting ≤5, 9, and 10 hours of sleep and reporting a history of hypertension were at 60% (95% CI: 1.53-1.67), 57% (95% CI: 1.50-1.65), and 92% (95% CI: 1.79-2.06) increased risk of mortality, respectively (Table 22). Compared to the reference group, those reporting ≥10 hours of sleep and having no history of hypertension was at a 43% (95% CI: 1.33-1.54) increased risk of mortality. Similar synergistic associations were observed for cardiovascular and stroke mortality.

Compared to participants reporting 7 hours of sleep and without a history of diabetes at baseline, those with a history of diabetes had a greater than 100% higher risk of mortality, regardless of sleep duration (Table 23). The strongest associations were observed among diabetic

participants who reported ≤5 (HR: 2.24, 95% CI: 2.12-2.38), 9 (HR: 2.04, 1.94-2.13), and ≥10 hours (HR: 2.81, 95% CI: 2.56-3.07) of sleep. Even among participants without diabetes, ≥10 hours of sleep were associated with a 40% increased risk of mortality (95% CI: 1.32-1.48). The synergistic association between sleep and diabetes was similar for cardiovascular and stroke mortality.

4.5 Discussion

In this study based on a large, ethnically diverse population, a higher risk of death in participants who reported extreme short and long sleep was detected. In addition, the J-shaped association was seen consistently across age, sex, and ethnicity. While we expected to see differences by BMI categories, hypertension status, and diabetes status, findings were consistent across the subgroups. Findings from this study agrees with previous reports. In the Japan Public Health Center (JPHC) prospective study with similar follow-up duration as this study, ≤5, 8, 9, and ≥10 hours of sleep, compared to 7 hours, was associated with a higher risk of mortality [207]. Among male participants, mortality risk associated with ≤5, 8, 9, and ≥10 hours of sleep were 1.15 (95% CI: 1.07-1.23), 1.06 (95% CI: 1.03-1.10), 1.13 (95% CI: 1.07-1.20), and 1.34 (95% CI: 1.26-1.44), respectively, while HRs among women were 1.07 (95% CI: 1.07-1.15), 1.07 (95% CI: 1.02-1.12), 1.17 (95% CI: 1.09-1.25), and 1.48 (95% CI: 1.36-1.61). Their findings on cardiovascular mortality were similar to ours as well. Our results were also consistent with findings from a Shanghai cohort study, in which the HRs associated with all-cause mortality were 1.11 (95% CI: 1.00-1.23), 1.15 (95% CI: 1.05-1.26), 1.34 (95% CI: 1.17-1.54), and 1.81 (95% CI: 1.59-2.06) in participants reporting ≤5, 8, 9, and ≥10 hours of sleep, respectively [41].

The causal mechanism between sleep and mortality is understudied and unknown. However, our findings are biologically plausible, as there is evidence suggesting that deviations from recommended sleep duration increases the activity of the sympathetic nervous system, increase secretions of proinflammatory cytokines, and disrupts other metabolic and endocrine functions that can result in higher mortality risk [121, 124, 185, 199, 223]. Like many previous studies, we found that long sleep was associated with a higher risk of mortality than short sleep [29, 41, 192, 200, 207]. Although our study was not able to uncover the reasons for this disparity, we offer several hypotheses. First, it is possible there is a true, causal association between long sleep and mortality that is different from mechanisms linking short sleep with mortality. Another possibility is that findings on long sleep so far are confounded. As long sleep is often associated with fatigue and lethargy, which are indicators for poor physical health. These individuals may have functional limitations due to chronic disease and may live more sedentary lifestyles, often inactive in bed. In addition, this extended time in bed may be misreported as physiological sleep. In contrast, short sleep may be representative of a healthier, more active lifestyle. Therefore, the disparities in mortality risk may be partially explained by lifestyle factors and the presence of subclinical disease associated with sleep behaviors.

Although our findings are consistent with previous studies, we are unable to rule out the presence of residual confounding. There were sleep factors unmeasured in this study, such as the presence of obstructive sleep apnea and sleep fragmentation, as well as the use of sleep medications and hypnotics, which are known risk factors for mortality [168, 201, 224-226]. There are only a few reports that found an independent association between sleep duration and mortality after adjusting for some of these factors [195, 203]. Our findings could have also been confounded by physical and psychosocial health status, as previous reports have found stronger

sleep-mortality associations among individuals with poor health or reporting numerous medical conditions [40, 190, 205, 227]. In contrast, other reports have indicated an independent association between sleep duration and mortality even after accounting for health indices and pre-existing conditions [41, 192, 204].

In this study, the association between sleep duration and mortality was slightly higher in participants aged 45-54 years, compared to those who were older. Using a cut-off of 50 years, the JPHC study found similar results, in which the HRs associated with ≤5 and ≥10 hours of sleep among younger men were 1.59 (95% CI: 1.21-2.09) and 1.95 (95% CI: 1.41-1.59), respectively, while the HRs among older men for the corresponding sleep categories were 1.41 (95% CI: 1.15-1.72) and 1.61 (95% CI: 1.38-1.87) [200]. Our study also found similar trends of higher risk estimates in the youngest group for cardiovascular and stroke mortality, but the JPHC study did not find clear differences by age.

In our study, we did not find any differences in all-cause and cardiovascular mortality by sex. In a previous study conducted in Shanghai, the risk of all-cause and cardiovascular mortality was similar across sex, except in those reporting ≥10 hours of sleep, where higher estimates were seen in women (all-cause: HR – 2.11, 95% CI: 1.77-2.52; CVD: HR – 2.64, 95% CI: 1.99-3.52) compared to men (all-cause: HR – 1.55, 95% CI: 1.29-1.86; CVD: HR – 1.58, 95% CI: 1.14-2.18) [41]. In comparison, several studies have concluded no differences across sex [29, 191, 193, 200].

Our study is unique in that it is one of the only studies to assess ethnic differences of the sleep-mortality relationship. We found a consistent J-shaped association between sleep duration and mortality across ethnic groups. The only study that investigated ethnic differences was a

previous MEC study that looked at data between 1993 and 2007 and found that ethnicity was not an effect modifier (p-interaction = 0.34) [29].

We investigated the role of obesity in the sleep-mortality relationship by examining differences across BMI groups and by assessing the combined effect of sleep and BMI. Our stratified analyses indicated that, except for extreme long sleepers, the association between sleep duration and mortality was consistently higher among those with normal BMI, which was could have been likely due to the lower baseline risk of mortality in this group. Our results were consistent with the JPHC study that found higher risks of mortality in those with BMI <25 kg/m^2, compared to those ≥25kg/m^2 [200]. We also investigated the potential synergistic effect of sleep duration and obesity and found that obese participants reporting extreme short and long sleep was at a much higher risk for mortality, compared to participants with normal BMI and 7 hours of sleep. Our findings also agreed with the NIH-AARP study, where participants reporting <7 hours of sleep and had BMI ≥25 kg/m^2 were at highest risk of all-cause (HR: 1.11, 95% CI: 1.08-1.15) and cardiovascular mortality (HR: 1.33, 95% CI: 1.26-1.40), compared to participants who reported 7-8 hours of sleep and had BMI under 25 kg/m^2 [40]. Although we reported strong associations among underweight participants, we hesitate to make conclusive remarks because the number of participants in this group was relatively small. In addition, we also cannot rule out that these participants do not have prevalent disease which was not adequately accounted for in our analysis.

In this study, we reported a synergistic effect of poor sleep and hypertension on mortality risk. Among all sleep and hypertension combinations, those with hypertension and reporting extreme short or long sleep were at highest risk of mortality. We believe that our study is one of the first to investigate the combined effects of sleep and hypertension on mortality. The only

similar study we found is a study based on the Penn State Adult Cohort, which found that sleep duration modified the association between cardiometabolic risk factors and mortality [228]. However, this study looked a variety of cardiometabolic risk factors, such as diabetes, alcohol consumption, and depression and did not report any interactions between sleep duration and hypertension alone. Our findings on the joint effects of sleep duration and diabetes were consistent with previous reports [229]. In a previous NHIS study, participants with diabetes and reporting ≥10 hours of sleep were at a 117% increased risk (95% CI: 1.72-2.73) of mortality compared to participants with no diabetes and reporting 7 hours of sleep [230]. Similar to our findings, the next highest estimates were observed among participants with diabetes and reporting ≤5 and 9 hours of sleep. There is also a report using the UK Biobank found that the presence of both diabetes and frequent sleep disturbances was associated with greater risk of all-cause mortality than either condition alone [231].

4.5.1 Strengths and Limitations

This study was based on a large ethnically diverse population with a mean follow-up time much longer than many previous studies [29, 40, 41, 190, 192, 193, 202, 203, 205]. The large sample size allowed for subgroup analyses, which was important in investigating the potential disparities of the sleep-mortality relationship. These subgroup analyses add to the uniqueness of our study, as it is rarely seen in sleep literature. This study also adjusted for a wide range of covariates that were associated with sleep duration and mortality. Sleep duration information was collected prior to any death events, minimizing recall bias. Additional analysis excluding early cases was also conducted because any effect that sleep may have on mortality risk, if any, would not have occurred immediately, which would increase the likelihood of early deaths being explained by other unadjusted factors.

This study also comes with several limitations. The first limitation is that information on sleep duration was self-reported at one point in time only. Previous papers have reported inconsistent findings on the correlation between subjective and objective sleep measurements [133-135]. Due to the nature of the sleep question in the questionnaire, it was not possible to discern whether participants were reporting nocturnal sleep or total sleep duration over a 24-hour period. Next, there is a possibility of misdiagnosis of deaths due to cardiovascular and stroke causes. However, it is unlikely for this misclassification to differentially be related to sleep information. In the case of non-differential misclassification of a dichotomous outcome, the association would bias toward the null, suggesting that the estimates in this study are conservative. In addition, findings about the association between cardiovascular and stroke mortality may be biased due to informative censoring arising from competing risks. Survival analysis using the Cox proportional hazard model assume independent censoring, which assume that participants who remain under follow-up have the same future risk for the occurrence of the event as those no longer being followed. This is an issue in our study, because participants who have died from other causes other than the primary outcome (example: stroke mortality) are no longer at risk of this primary outcome.

In addition, residual confounding could not be ruled out in this study. The MEC did not collect information on other sleep characteristics, such as sleep quality, chronotype, and sleep disorders, which are known risk factors for all-cause and cardiovascular mortality [201, 203]. Information on the use of sleep medications and hypnotics and other drugs affecting sleep behavior and quality was also not available in this study. In a previous study examining the Women's Health Initiative participants, the use of nonbenzodiazepine GABA agonists and hypnotics was associated with a higher risk of total and cardiovascular mortality [226].

Adjustment for socioeconomic status in this study may have been lacking, due to missing income and job type information in many participants. This is important because shift work, particularly at night, is known to be a risk factor for early mortality [232]. Having information on employment status and job type could have also helped explain the disparity in mortality risk between short and long sleepers, as some job types may be associated shorter sleep durations and a healthier and wealthier lifestyle. Finally, physical and psychosocial health, as well as other pre-existing health conditions, are potential confounders that was unavailable in this study. There are numerous reports, however, of an independent association between sleep duration and mortality even after adjustment for physical health, depression, and other pre-existing health conditions [40, 190, 205, 227].

4.6 Conclusion

In this study that examined a population of middle-aged and elderly adults in Hawai'i and L.A., extreme short sleep, long sleep, and extreme long sleep were found to increase the risk for all-cause, cardiovascular, and stroke mortality. These results add to the available literature and consider the role of other factors that may modify the association between sleep duration and mortality. Our study revealed that age and BMI may be potential effect modifiers, and we also reported a potential synergistic association between poor sleep and high BMI. Based on this finding, future studies examining the role of sleep on mortality risk should consider the potential for other synergistic effects with other mortality risk factors.

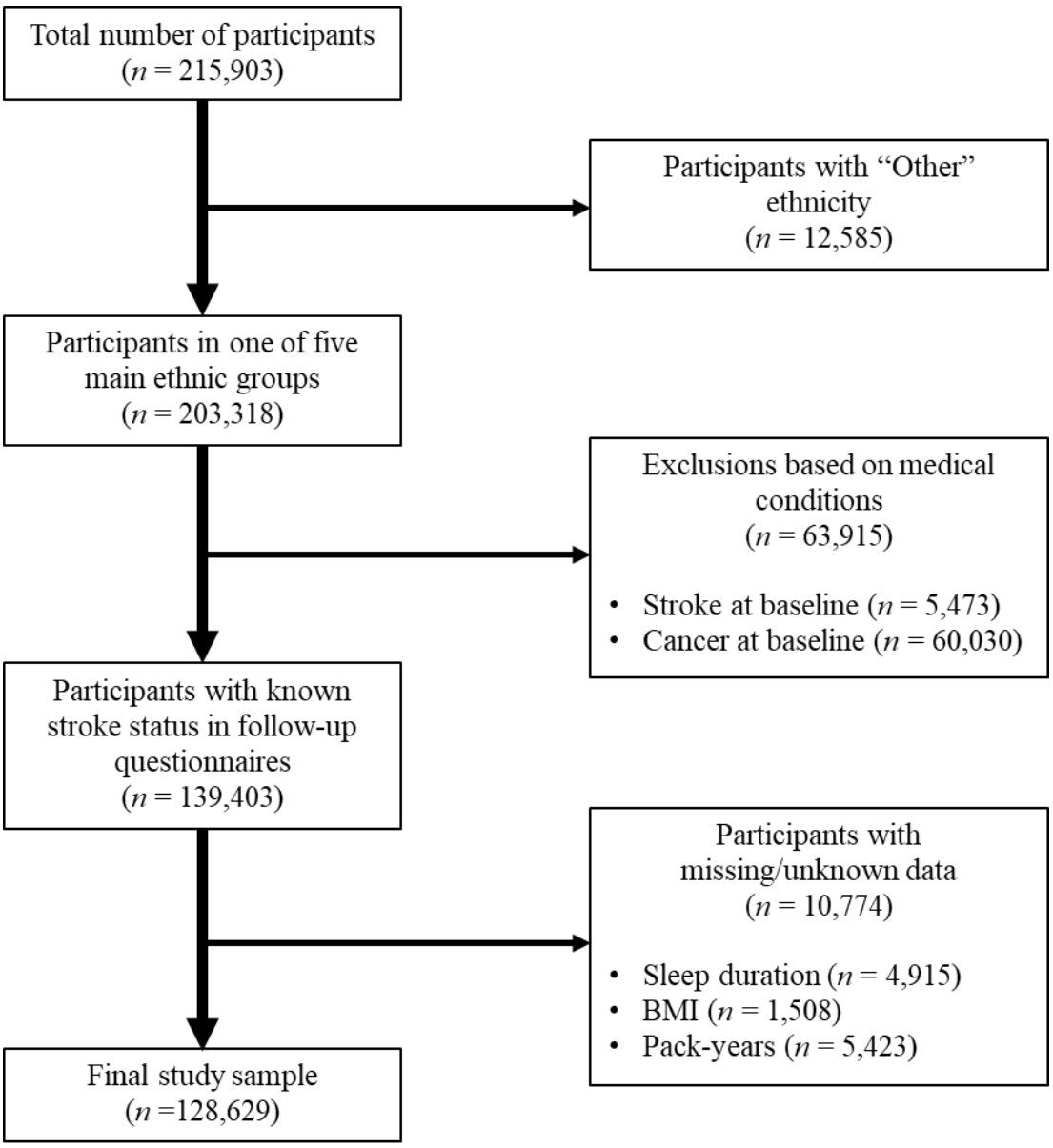

Figure 6. Exclusion criteria to analyze the association between sleep duration and mortality in the MEC, 1993–2016.

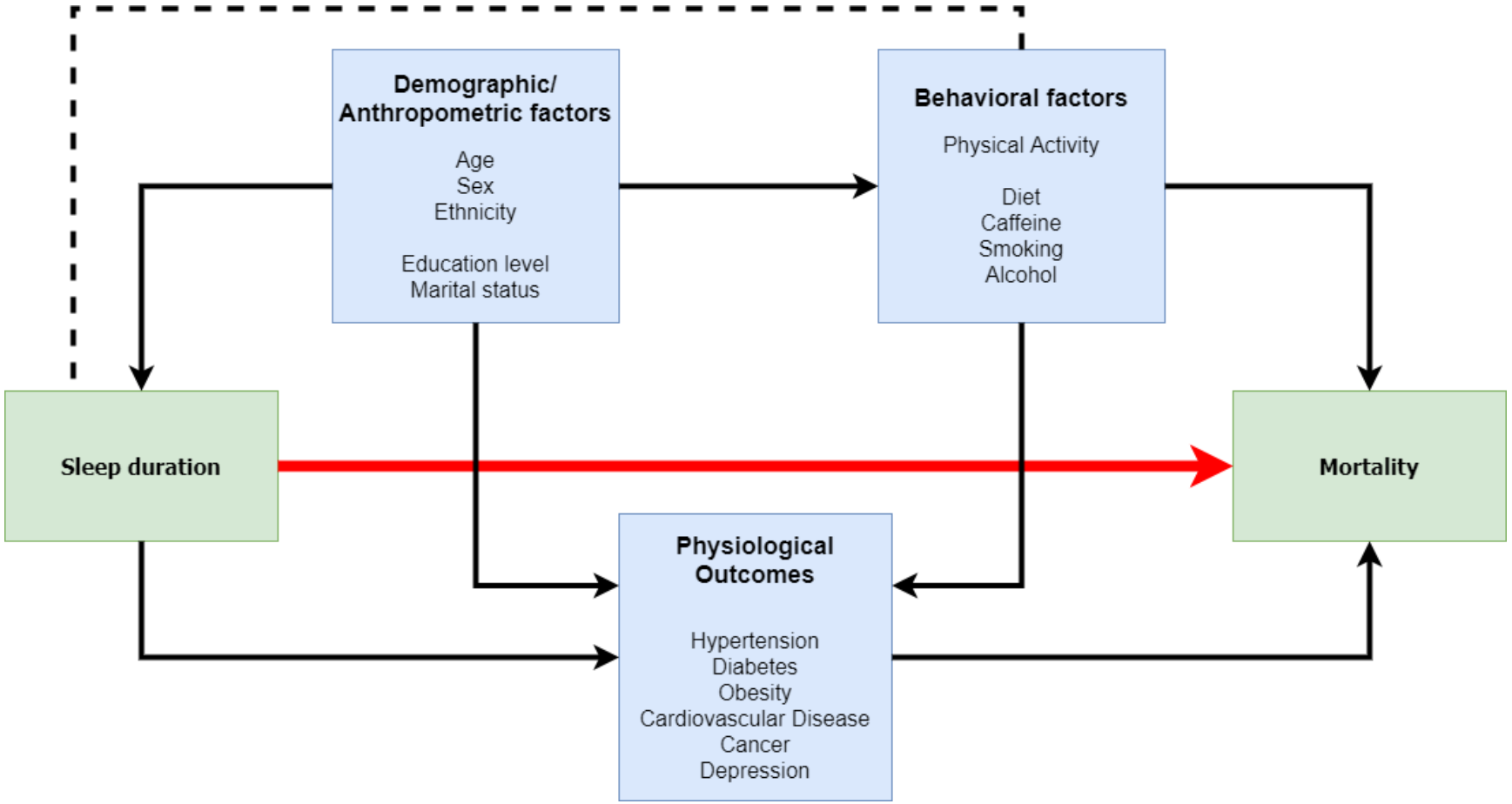

Figure 7. Causal diagram representing the relationship between sleep duration, mortality, and confounding variables. Dotted lines represent an association between factors and arrows represent causal direction.

Table 16. Demographic characteristics at the baseline questionnaire of the final study sample to analyze the association between sleep duration and mortality.

		Sleep Duration (Hours)						
	All (*n*)	**≤5**	**6**	**7**	**8**	**9**	**≥10**	***p*[e]**
Number of Participants	128,629	12,516 (9.7%)	31,581 (24.6%)	40,967 (31.9%)	32,271 (25.1%)	8,402 (6.5%)	2,892 (2.2%)	
Age (years)[a]								<0.0001
45-54	46,839	4,262 (9.1%)	12,223 (26.1%)	15,760 (33.6%)	11,039 (23.6%)	2,671 (5.7%)	884 (1.9%)	
55-64	42,473	4,149 (9.8%)	10,309 (24.3%)	13,568 (31.9%)	10,776 (25.4%)	2,706 (6.4%)	965 (2.2%)	
≥65	39,317	4,105 (10.4%)	9,049 (23.0%)	11,639 (29.6%)	10,456 (26.6%)	3,025 (7.7%)	1,043 (2.7%)	
Sex[a]								<0.0001
Male	55,418	4,743 (8.6%)	13,602 (24.5%)	17,923 (32.3%)	14,085 (25.4%)	3,726 (6.7%)	1,339 (2.4%)	
Female	73,211	7,773 (10.6%)	17,979 (24.6%)	23,044 (31.5%)	18,186 (24.8%)	4,676 (6.4%)	1,553 (2.1%)	
Ethnicity[a]								<0.0001
White	32,638	1,769 (5.4%)	6,268 (19.2%)	11,433 (35.0%)	9,961 (30.5%)	2,642 (8.1%)	565 (1.8%)	
African American	19,371	3,123 (16.1%)	5,028 (26.0%)	4,780 (24.7%)	4,383 (22.6%)	1,360 (7.0%)	697 (3.6%)	
Native Hawaiian	9,017	1,279 (14.2%)	2,479 (27.5%)	2,503 (27.8%)	1,971 (21.8%)	524 (5.8%)	261 (2.9%)	
Japanese American	37,245	3,155 (8.5%)	11,037 (29.6%)	13,302 (35.7%)	7,783 (20.9%)	1,551 (4.2%)	417 (1.1%)	
Latino	30,358	3,190 (10.5%)	6,769 (22.3%)	8,949 (29.5%)	8,173 (26.9%)	2,325 (7.7%)	952 (3.1%)	
Education[a]								<0.0001
≤12 years	54,459	6,629 (12.2%)	12,594 (23.1%)	15,535 (28.5%)	13,991 (25.7%)	3,992 (7.3%)	1,718 (3.2%)	
13-15 years	38,289	3,461 (9.0%)	9,858 (25.8%)	12,353 (32.3%)	9,401 (24.5%)	2,478 (6.5%)	738 (1.9%)	
≥16 years	35,345	2,355 (6.7%)	9,021 (25.5%)	12,940 (36.6%)	8,734 (24.7%)	1,889 (5.3%)	406 (1.2%)	
Missing	536	71 (13.2%)	108 (20.2%)	139 (25.9%)	145 (27.1%)	43 (8.0%)	30 (5.6%)	
Marital status[a]								<0.0001
Married	85,258	7,035 (8.3%)	20,444 (24.0%)	28,359 (33.3%)	22,003 (25.8%)	5,667 (6.6%)	1,750 (2.0%)	
Not married	42,422	5,367 (12.7%)	10,917 (25.7%)	12,339 (29.1%)	10,023 (23.6%)	2,665 (6.3%)	1,111 (2.6%)	
Missing	949	114 (12.0%)	220 (23.2%)	269 (28.3%)	245 (25.8%)	70 (7.4%)	31 (3.3%)	
BMI (kg/m^2)[a,c]								<0.0001
Underweight	2,296	249 (10.8%)	591 (25.7%)	720 (31.4%)	535 (23.3%)	138 (6.0%)	63 (2.8%)	
Normal	51,940	4,129 (8.0%)	12,653 (24.4%)	18,039 (34.7%)	13,131 (25.3%)	3,134 (6.0%)	854 (1.6%)	
Overweight	48,748	4,788 (9.8%)	12,114 (24.9%)	15,230 (31.2%)	12,331 (25.3%)	3,227 (6.6%)	1,058 (2.2%)	

Obese	25,645	3,350 (13.0%)	6,223 (24.3%)	6,978 (27.2%)	6,274 (24.5%)	1,903 (7.4%)	917 (3.6%)	
Smoking status[a]								<0.0001
Never	60,866	6,093 (10.0%)	15,257 (25.1%)	19,710 (32.4%)	15,024 (24.7%)	3,640 (6.0%)	1,142 (1.8%)	
Yes, quit	48,258	4,297 (8.9%)	11,509 (23.8%)	15,474 (32.1%)	12,487 (25.9%)	3,369 (7.0%)	1,122 (2.3%)	
Yes, current	19,505	2,126 (10.9%)	4,815 (24.7%)	5,783 (29.7%)	4,760 (24.4%)	1,393 (7.1%)	628 (3.2%)	
Smoking pack-years[b]	9.1 ± 14.1	8.4 ± 13.7	8.8 ± 13.8	8.9 ± 13.9	9.4 ± 14.3	10.8 ± 15.5	11.5 ± 16.0	<0.0001
Alcohol consumption (g/day)[a]								<0.0001
<2.32 (men), 0 (women)	70,042	7,446 (10.6%)	17,776 (25.4%)	21,657 (30.9%)	17,102 (24.4%)	4,392 (6.3%)	1,669 (2.4%)	
≥2.32 (men), >0 (women)	53,817	4,313 (8.0%)	12,670 (23.6%)	18,104 (33.6%)	14,011 (26.0%)	3,698 (6.9%)	1,021 (1.9%)	
Missing	4,770	757 (15.9%)	1,135 (23.8%)	1,206 (25.3%)	1,158 (24.3%)	312 (6.5%)	202 (4.2%)	
Caffeine consumption (mg/day)[a]								<0.0001
<100	63,757	6,551 (10.3%)	15,605 (24.5%)	19,915 (31.2%)	16,055 (25.2%)	4,164 (6.5%)	1,467 (2.3%)	
100-<200	25,513	2,265 (8.9%)	6,080 (23.8%)	8,252 (32.3%)	6,621 (26.0%)	1,743 (6.8%)	552 (2.2%)	
≥200	34,589	2,943 (8.5%)	8,761 (25.3%)	11,594 (33.5%)	8,437 (24.4%)	2,183 (6.3%)	671 (2.0%)	
Missing	4,770	757 (15.9%)	1,135 (23.8%)	1,206 (25.3%)	1,158 (24.3%)	312 (6.5%)	202 (4.2%)	
DASH score[a]								<0.0001
8-21	35,845	3,861 (10.8%)	9,421 (26.3%)	11,113 (31.0%)	8,343 (23.3%)	2,236 (6.2%)	871 (2.4%)	
22-24	30,375	2,981 (9.8%)	7,543 (24.9%)	9,607 (31.6%)	7,572 (24.9%)	1,977 (6.5%)	695 (2.3%)	
25-27	29,447	2,704 (9.2%)	7,005 (23.8%)	9,573 (32.5%)	7,621 (25.9%)	1,971 (6.7%)	573 (1.9%)	
≥28	28,192	2,213 (7.8%)	6,477 (23.0%)	9,468 (33.6%)	7,577 (26.9%)	1,906 (6.8%)	551 (1.9%)	
Missing	4,770	757 (15.9%)	1,135 (23.8%)	1,206 (25.3%)	1,158 (24.3%)	312 (6.5%)	202 (4.2%)	
Physical activity (MET-hours/day)[a,d]								<0.0001
0.1-1.97 (men), 0.1-1.43 (women)	37,555	4,600 (12.3%)	9,209 (24.5%)	10,630 (28.3%)	9,280 (24.7%)	2,625 (7.0%)	1,211 (3.2%)	
1.98-4.77 (men), 1.44-2.86 (women)	26,523	2,419 (9.1%)	6,810 (25.7%)	8,691 (32.8%)	6,459 (24.4%)	1,654 (6.2%)	490 (1.8%)	
4.78-8.86 (men), 2.87-6.40 (women)	28,547	2,296 (8.1%)	7,082 (24.8%)	9,773 (34.2%)	7,146 (25.0%)	1,771 (6.2%)	479 (1.7%)	
≥8.87 (men), ≥6.41 (women)	30,415	2,466 (8.1%)	7,191 (23.7%)	10,259 (33.7%)	7,917 (26.0%)	2,012 (6.6%)	570 (1.9%)	
Missing	5,589	735 (13.1%)	1,289 (23.1%)	1,614 (28.9%)	1,469 (26.3%)	340 (6.1%)	142 (2.5%)	
History of hypertension[a]								<0.0001
No	80,849	6,994 (8.6%)	19,613 (24.3%)	26,970 (33.4%)	20,608 (25.5%)	5,081 (6.3%)	1,583 (1.9%)	
Yes	47,780	5,522 (11.6%)	11,968 (25.1%)	13,997 (29.3%)	11,663 (24.4%)	3,321 (6.9%)	1,309 (2.7%)	
History of diabetes[a]								<0.0001

No	114,274	10,698 (9.4%)	28,243 (24.7%)	37,098 (32.5%)	28,682 (25.1%)	7,272 (6.3%)	2,281 (2.0%)
Yes	14,355	1,818 (12.7%)	3,338 (23.2%)	3,869 (26.9%)	3,589 (25.0%)	1,130 (7.9%)	611 (4.3%)

[a]n (row %).
[b]mean ± SD.
[c]underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–30 kg/m^2), and obese (≥30 kg/m^2).
[d]METs for moderate and vigorous activity per day.
[e]p values calculated by analysis of variance and χ^2 test.

Table 17. Estimated associations (hazard ratios [HRs] and 95% confidence intervals [CIs]) between self-reported sleep duration and all-cause mortality; overall model and stratified models by age, sex, ethnicity, BMI, history of hypertension, and history of diabetes.

		Hours of Sleep					
		≤5	**6**	**7**	**8**	**9**	**≥10**
	No. of events/No. of participants	5,954/12,516	12,274/31,581	15,304/40,967	13,760/32,271	4,079/8,402	1,681/2,892
		HR (95% CI)					
Overall[a]	53,052/128,629	1.12 (1.09-1.16)	1.02 (0.99-1.04)	1.00	1.04 (1.02-1.07)	1.13 (1.09-1.17)	1.39 (1.32-1.46)
Age Group[b]							
45-54	6,860/46,839	1.25 (1.16-1.36)	1.07 (1.01-1.15)	1.00	1.11 (1.04-1.19)	1.29 (1.17-1.43)	1.55 (1.35-1.77)
55-64	15,953/42,473	1.11 (1.05-1.18)	1.04 (0.99-1.08)	1.00	1.04 (0.99-1.08)	1.12 (1.05-1.19)	1.33 (1.22-1.46)
≥65	30,239/39,317	1.07 (1.03-1.12)	1.00 (0.97-1.03)	1.00	1.03 (1.00-1.06)	1.11 (1.06-1.16)	1.37 (1.28-1.47)
Sex[b]							
Male	25,670/55,418	1.12 (1.07-1.18)	1.01 (0.98-1.05)	1.00	1.05 (1.01-1.08)	1.13 (1.07-1.18)	1.34 (1.25-1.44)
Female	27,382/73,211	1.13 (1.08-1.17)	1.03 (1.00-1.07)	1.00	1.04 (1.00-1.07)	1.14 (1.08-1.19)	1.44 (1.34-1.55)
Ethnicity[b]							
White	13,315/32,638	1.14 (1.06-1.23)	1.04 (0.99-1.10)	1.00	0.99 (0.95-1.04)	1.10 (1.03-1.17)	1.40 (1.26-1.56)
African American	10,494/19,371	1.08 (1.01-1.15)	0.98 (0.93-1.04)	1.00	1.03 (0.98-1.09)	1.15 (1.06-1.25)	1.29 (1.16-1.42)
Native Hawaiian	3,536/9,017	1.20 (1.08-1.33)	0.98 (0.89-1.08)	1.00	1.12 (1.02-1.24)	1.23 (1.06-1.42)	1.32 (1.10-1.58)
Japanese American	13,942/37,245	1.13 (1.06-1.20)	1.04 (1.00-1.09)	1.00	1.10 (1.05-1.15)	1.19 (1.10-1.28)	1.68 (1.48-1.90)
Latino	11,765/30,358	1.09 (1.03-1.17)	1.00 (0.95-1.05)	1.00	1.04 (0.99-1.09)	1.06 (0.99-1.14)	1.32 (1.19-1.45)
BMI (kg/m^2)[b]							
Underweight	1,267/2,296	0.94 (0.77-1.15)	1.03 (0.88-1.20)	1.00	1.07 (0.92-1.25)	1.17 (0.91-1.50)	1.51 (1.11-2.06)
Normal	20,137/51,940	1.22 (1.16-1.28)	1.03 (0.99-1.07)	1.00	1.06 (1.02-1.10)	1.17 (1.10-1.24)	1.46 (1.33-1.60)
Overweight	19,727/48,748	1.09 (1.03-1.14)	1.01 (0.97-1.05)	1.00	1.04 (1.00-1.08)	1.11 (1.05-1.17)	1.39 (1.28-1.52)
Obese	11,921/25,645	1.08 (1.02-1.15)	1.02 (0.97-1.07)	1.00	1.02 (0.97-1.07)	1.12 (1.04-1.20)	1.28 (1.17-1.40)
History of Hypertension[b]							
No	26,834/80,849	1.11 (1.06-1.16)	1.03 (0.99-1.06)	1.00	1.05 (1.02-1.08)	1.15 (1.10-1.21)	1.44 (1.34-1.55)
Yes	26,218/47,780	1.13 (1.08-1.18)	1.01 (0.98-1.04)	1.00	1.04 (1.00-1.07)	1.11 (1.06-1.17)	1.34 (1.25-1.44)
History of Diabetes[b]							
No	42,972/114,274	1.13 (1.09-1.17)	1.03 (1.00-1.05)	1.00	1.04 (1.01-1.07)	1.13 (1.09-1.17)	1.40 (1.32-1.49)

Yes	10,080/14,355	1.07 (1.00-1.15)	0.98 (0.93-1.04)	1.00	1.06 (1.00-1.12)	1.16 (1.07-1.25)	1.33 (1.21-1.47)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, marital status, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, history of hypertension, and history of diabetes.
[b]adjusted for all other variables.

Table 18. Estimated associations (hazard ratios [HRs] and 95% confidence intervals [CIs]) between self-reported sleep duration and cardiovascular mortality; overall model and stratified models by age, sex, ethnicity, BMI, history of hypertension, and history of diabetes.

		Hours of Sleep					
		≤5	**6**	**7**	**8**	**9**	**≥10**
	No. of events/No. of participants	2,913/12,516	5,747/31,581	6,987/40,967	6,582/32,271	1,904/8,402	832/2,892
		HR (95% CI)					
Overall[a]	24,965/128,629	1.14 (1.10-1.20)	1.03 (0.99-1.06)	1.00	1.08 (1.04-1.12)	1.13 (1.08-1.19)	1.42 (1.32-1.53)
Age Group[b]							
45-54	3,054/46,839	1.33 (1.18-1.50)	1.09 (0.98-1.20)	1.00	1.24 (1.12-1.37)	1.28 (1.09-1.49)	1.72 (1.42-2.09)
55-64	7,379/42,473	1.10 (1.01-1.19)	1.04 (0.97-1.11)	1.00	1.05 (0.99-1.12)	1.20 (1.09-1.32)	1.31 (1.15-1.50)
≥65	14,532/39,317	1.10 (1.04-1.17)	1.00 (0.96-1.05)	1.00	1.06 (1.01-1.11)	1.08 (1.01-1.15)	1.39 (1.26-1.53)
Sex[b]							
Male	12,477/55,418	1.14 (1.07-1.22)	1.00 (0.95-1.05)	1.00	1.08 (1.03-1.13)	1.16 (1.08-1.24)	1.37 (1.24-1.51)
Female	12,488/73,211	1.15 (1.09-1.22)	1.05 (1.00-1.11)	1.00	1.09 (1.03-1.14)	1.11 (1.03-1.19)	1.49 (1.34-1.65)
Ethnicity[b]							
White	5,750/32,638	1.22 (1.09-1.36)	1.05 (0.97-1.13)	1.00	1.03 (0.97-1.10)	1.11 (1.01-1.22)	1.35 (1.14-1.59)
African American	5,492/19,371	1.08 (0.99-1.18)	0.98 (0.91-1.06)	1.00	1.09 (1.01-1.18)	1.16 (1.04-1.30)	1.36 (1.19-1.56)
Native Hawaiian	1,783/9,017	1.20 (1.03-1.39)	1.00 (0.87-1.14)	1.00	1.11 (0.97-1.27)	1.09 (0.89-1.35)	1.37 (1.07-1.76)
Japanese American	6,300/37,245	1.17 (1.07-1.28)	1.07 (1.00-1.14)	1.00	1.14 (1.07-1.22)	1.22 (1.09-1.37)	1.85 (1.54-2.21)
Latino	5,640/30,358	1.10 (1.00-1.20)	0.99 (0.91-1.06)	1.00	1.04 (0.97-1.12)	1.03 (0.93-1.15)	1.27 (1.10-1.46)
BMI (kg/m^2)[b]							
Underweight	502/2,296	1.04 (0.75-1.43)	1.19 (0.93-1.52)	1.00	1.39 (1.08-1.78)	1.67 (1.15-2.43)	1.43 (0.87-2.34)
Normal	8,837/51,940	1.24 (1.15-1.34)	1.02 (0.97-1.08)	1.00	1.09 (1.03-1.16)	1.12 (1.03-1.28)	1.53 (1.34-1.74)
Overweight	9,604/48,748	1.15 (1.07-1.23)	1.03 (0.98-1.09)	1.00	1.09 (1.03-1.15)	1.12 (1.03-1.21)	1.40 (1.24-1.58)
Obese	6,022/25,645	1.06 (0.97-1.15)	1.00 (0.93-1.07)	1.00	1.04 (0.97-1.12)	1.14 (1.04-1.27)	1.31 (1.15-1.48)
History of Hypertension[b]							
No	11,305/80,849	1.11 (1.03-1.19)	1.03 (0.98-1.09)	1.00	1.11 (1.06-1.16)	1.14 (1.06-1.23)	1.43 (1.28-1.60)
Yes	13,660/47,780	1.17 (1.10-1.24)	1.02 (0.97-1.07)	1.00	1.06 (1.01-1.11)	1.13 (1.05-1.21)	1.41 (1.28-1.55)
History of Diabetes[b]							

No	19,987/114,274	1.18 (1.12-1.24)	1.04 (1.00-1.08)	1.00	1.10 (1.06-1.14)	1.15 (1.08-1.21)	1.42 (1.31-1.55)
Yes	4,978/14,355	1.02 (0.92-1.12)	0.98 (0.90-1.06)	1.00	1.01 (0.94-1.10)	1.09 (0.97-1.21)	1.36 (1.18-1.55)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, marital status, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, history of hypertension, and history of diabetes.
[b]adjusted for all other variables.

Table 19. Estimated associations (hazard ratios [HRs] and 95% confidence intervals [CIs]) between self-reported sleep duration and stroke mortality; overall model and stratified models by age, sex, ethnicity, BMI, history of hypertension and history of diabetes.

		Hours of Sleep					
		≤5	**6**	**7**	**8**	**9**	**≥10**
	No. of events/No. of participants	530/12,516	1,126/31,581	1,401/40,967	1,275/32,271	370/8,402	154/2,892
		HR (95% CI)					
Overall[a]	4,856/128,629	1.10 (0.99-1.21)	1.02 (0.94-1.10)	1.00	1.08 (1.00-1.17)	1.18 (1.05-1.32)	1.53 (1.30-1.81)
Age Group[b]							
45-54	464/46,839	1.25 (0.91-1.72)	1.04 (0.81-1.35)	1.00	1.38 (1.08-1.78)	1.26 (0.85-1.89)	1.66 (0.98-2.81)
55-64	1,437/42,473	1.10 (0.91-1.33)	1.04 (0.90-1.20)	1.00	1.05 (0.91-1.21)	1.16 (0.93-1.43)	1.41 (1.04-1.91)
≥65	2,955/39,317	1.06 (0.93-1.21)	1.01 (0.91-1.12)	1.00	1.06 (0.96-1.16)	1.18 (1.02-1.36)	1.55 (1.25-1.93)
Sex[b]							
Male	2,016/55,418	1.16 (0.99-1.37)	1.00 (0.89-1.14)	1.00	1.10 (0.98-1.23)	1.21 (1.02-1.44)	1.48 (1.15-1.90)
Female	2,840/73,211	1.07 (0.94-1.21)	1.02 (0.93-1.13)	1.00	1.07 (0.97-1.18)	1.15 (0.98-1.35)	1.57 (1.25-1.97)
Ethnicity[b]							
White	1,025/32,638	1.27 (0.98-1.63)	1.01 (0.84-1.21)	1.00	1.01 (0.86-1.18)	1.07 (0.85-1.35)	1.71 (1.18-2.48)
African American	972/19,371	1.01 (0.82-1.23)	0.91 (0.76-1.09)	1.00	1.05 (0.87-1.25)	1.08 (0.83-1.40)	1.21 (0.86-1.71)
Native Hawaiian	289/9,017	1.12 (0.77-1.63)	1.05 (0.76-1.46)	1.00	1.09 (0.78-1.53)	0.89 (0.50-1.58)	2.08 (1.20-3.60)
Japanese American	1,493/37,245	1.18 (0.98-1.43)	1.12 (0.99-1.28)	1.00	1.17 (1.01-1.34)	1.45 (1.16-1.81)	1.81 (1.22-2.69)
Latino	1,077/30,358	0.94 (0.76-1.18)	0.92 (0.78-1.10)	1.00	1.04 (0.89-1.22)	1.12 (0.89-1.40)	1.32 (0.95-1.82)
BMI (kg/m^2)[b]							
Underweight	113/2,296	0.74 (0.36-1.52)	1.17 (0.72-1.91)	1.00	1.22 (0.74-2.02)	0.95 (0.36-2.46)	0.42 (0.06-3.12)
Normal	1,990/51,940	1.19 (1.01-1.40)	1.01 (0.90-1.14)	1.00	1.07 (0.95-1.21)	1.13 (0.93-1.36)	1.51 (1.12-2.04)
Overweight	1,803/48,748	1.11 (0.94-1.32)	1.06 (0.93-1.21)	1.00	1.18 (1.05-1.34)	1.24 (1.03-1.50)	1.88 (1.45-2.44)
Obese	950/25,645	0.97 (0.79-1.20)	0.92 (0.76-1.10)	1.00	0.91 (0.76-1.08)	1.17 (0.92-1.49)	1.18 (0.84-1.64)
History of Hypertension[b]							
No	2,305/80,849	1.12 (0.96-1.30)	1.05 (0.93-1.17)	1.00	1.13 (1.01-1.26)	1.21 (1.03-1.44)	1.33 (1.01-1.75)
Yes	2,551/47,780	1.08 (0.95-1.24)	0.99 (0.88-1.10)	1.00	1.04 (0.93-1.16)	1.15 (0.98-1.35)	1.67 (1.35-2.07)
History of Diabetes[b]							
No	4,097/114,274	1.13 (1.01-1.26)	1.02 (0.94-1.11)	1.00	1.11 (1.02-1.20)	1.23 (1.09-1.39)	1.53 (1.26-1.86)

Yes	759/14,355	0.96 (0.75-1.23)	0.97 (0.79-1.19)	1.00	0.95 (0.78-1.16)	0.95 (0.70-1.27)	1.44 (1.03-2.03)

[a]adjusted for age at cohort entry, sex, ethnicity, marital status, education level, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, history of hypertension, and history of diabetes.
[b]adjusted for all other variables.

Table 20. Estimated associations (hazard ratios [HRs] and 95% confidence intervals [CIs]) between self-reported sleep duration and mortality in a study sample with deaths that occurred within the first 3 years from cohort entry removed.

Outcome	**Hours of Sleep**					
	≤5	**6**	**7**	**8**	**9**	**≥10**
	HR (95% CI)[a]					
Total Mortality	1.10 (1.07-1.14)	1.02 (0.99-1.04)	1.00	1.04 (1.01-1.06)	1.12 (1.08-1.16)	1.37 (1.30-1.44)
Cardiovascular Mortality	1.13 (1.08-1.18)	1.02 (0.99-1.06)	1.00	1.07 (1.04-1.11)	1.12 (1.07-1.19)	1.41 (1.30-1.51)
Stroke Mortality	1.08 (0.97-1.20)	1.02 (0.94-1.10)	1.00	1.07 (0.99-1.16)	1.16 (1.03-1.30)	1.55 (1.31-1.84)

[a]adjusted for age at cohort entry, sex, ethnicity, marital status, education level, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, history of hypertension, and history of diabetes.

Table 21. Joint associations (hazard ratios [HRs] and 95% confidence intervals [CIs]) of self-reported sleep duration and BMI on the risk of all-cause, cardiovascular, and stroke mortality.

	Hours of Sleep					
	≤5	**6**	**7**	**8**	**9**	**≥10**
	HR (95% CI)[a]					
Total mortality						
Underweight	1.57 (1.33-1.85)	1.65 (1.48-1.85)	1.63 (1.47-1.81)	1.78 (1.58-1.99)	1.94 (1.56-2.43)	2.97 (2.25-3.91)
Normal	1.22 (1.16-1.29)	1.03 (0.99-1.07)	ref	1.06 (1.03-1.10)	1.18 (1.12-1.25)	1.50 (1.37-1.64)
Overweight	1.05 (1.00-1.10)	0.98 (0.94-1.02)	0.97 (0.94-1.01)	1.01 (0.97-1.05)	1.07 (1.01-1.13)	1.34 (1.23-1.46)
Obese	1.34 (1.27-1.42)	1.28 (1.22-1.34)	1.26 (1.20-1.31)	1.26 (1.21-1.32)	1.38 (1.29-1.47)	1.59 (1.45-1.73)
CVD mortality						
Underweight	1.39 (1.07-1.82)	1.58 (1.32-1.89)	1.38 (1.16-1.64)	1.87 (1.57-2.23)	2.13 (1.54-2.95)	2.31 (1.46-3.68)
Normal	1.27 (1.17-1.37)	1.03 (0.97-1.09)	ref	1.10 (1.04-1.16)	1.14 (1.04-1.25)	1.60 (1.40-1.83)
Overweight	1.16 (1.08-1.24)	1.05 (0.99-1.11)	1.02 (0.97-1.08)	1.11 (1.05-1.17)	1.14 (1.05-1.24)	1.42 (1.26-1.60)
Obese	1.43 (1.32-1.54)	1.37 (1.28-1.46)	1.37 (1.28-1.46)	1.40 (1.31-1.49)	1.53 (1.39-1.68)	1.76 (1.56-1.99)
Stroke mortality						
Underweight	1.00 (0.54-1.87)	1.54 (1.09-2.19)	1.35 (0.96-1.90)	1.61 (1.11-2.34)	1.25 (0.52-3.02)	0.67 (0.10-4.74)
Normal	1.19 (1.01-1.40)	1.02 (0.90-1.14)	ref	1.07 (0.96-1.21)	1.13 (0.93-1.36)	1.54 (1.14-2.07)
Overweight	0.99 (0.84-1.16)	0.95 (0.83-1.07)	0.90 (0.80-1.02)	1.06 (0.94-1.20)	1.12 (0.93-1.34)	1.68 (1.30-2.17)
Obese	1.15 (1.09-2.19)	1.09 (0.92-1.28)	1.17 (1.01-1.36)	1.05 (0.90-1.23)	1.34 (1.07-1.69)	1.39 (1.01-1.91)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, marital status, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, history of hypertension, and history of diabetes.

Table 22. Joint associations (hazard ratios [HRs] and 95% confidence intervals [CIs]) of self-reported sleep duration and hypertension on the risk of all-cause, cardiovascular, and stroke mortality.

	Hours of Sleep					
	≤5	**6**	**7**	**8**	**9**	**≥10**
	HR (95% CI)[a]					
Total mortality						
No Hypertension	1.11 (1.06-1.16)	1.03 (0.99-1.06)	ref	1.05 (1.02-1.09)	1.16 (1.10-1.22)	1.43 (1.33-1.54)
Hypertension	1.60 (1.53-1.67)	1.43 (1.38-1.48)	1.42 (1.37-1.46)	1.46 (1.42-1.51)	1.57 (1.50-1.65)	1.92 (1.79-2.06)
CVD mortality						
No Hypertension	1.12 (1.05-1.20)	1.03 (0.98-1.09)	ref	1.11 (1.06-1.17)	1.15 (1.07-1.24)	1.44 (1.29-1.61)
Hypertension	1.97 (1.86-2.09)	1.73 (1.65-1.82)	1.70 (1.62-1.79)	1.79 (1.71-1.88)	1.90 (1.78-2.04)	2.39 (2.18-2.63)
Stroke mortality						
No Hypertension	1.11 (0.95-1.29)	1.04 (0.93-1.17)	ref	1.13 (1.01-1.26)	1.22 (1.03-1.44)	1.31 (0.99-1.72)
Hypertension	1.78 (1.55-2.04)	1.62 (1.45-1.82)	1.64 (1.48-1.83)	1.70 (1.52-1.90)	1.88 (1.60-2.20)	2.78 (2.25-3.44)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, marital status, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, and history of diabetes.

Table 23. Joint associations (hazard ratios [HRs] and 95% confidence intervals [CIs]) of self-reported sleep duration and diabetes on the risk of all-cause, cardiovascular, and stroke mortality.

	Hours of Sleep					
	≤5	**6**	**7**	**8**	**9**	**≥10**
	HR (95% CI)[a]					
Total mortality						
No diabetes	1.13 (1.09-1.17)	1.03 (1.00-1.05)	ref	1.04 (1.02-1.07)	1.13 (1.09-1.18)	1.40 (1.32-1.48)
Diabetes	2.24 (2.12-2.38)	2.04 (1.94-2.13)	2.06 (1.98-2.15)	2.15 (2.06-2.24)	2.31 (2.16-2.48)	2.81 (2.56-3.07)
CVD mortality						
No diabetes	1.18 (1.13-1.24)	1.04 (1.00-1.08)	ref	1.10 (1.06-1.14)	1.16 (1.09-1.22)	1.43 (1.31-1.56)
Diabetes	2.14 (1.97-2.33)	2.07 (1.94-2.21)	2.12 (2.00-2.25)	2.11 (1.98-2.24)	2.21 (2.00-2.45)	2.89 (2.55-3.28)
Stroke mortality						
No diabetes	1.12 (1.00-1.25)	1.02 (0.94-1.11)	ref	1.11 (1.02-1.20)	1.23 (1.08-1.39)	1.52 (1.25-1.84)
Diabetes	1.69 (1.37-2.09)	1.69 (1.44-1.99)	1.75 (1.51-2.03)	1.64 (1.40-1.92)	1.63 (1.24-2.13)	2.65 (1.93-3.64)

[a]adjusted for age at cohort entry, sex, ethnicity, education level, marital status, BMI, smoking status, smoking pack-years, alcohol consumption, caffeine consumption, physical activity, DASH score, and history of hypertension.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 Introduction

Sleep duration is now considered one of many risk factors for disease and mortality, and it is now an important public health concern, especially with the increasing prevalence of short sleep worldwide [1, 3, 4, 6]. Both short and long sleep is associated with adverse health outcomes such as type 2 diabetes, obesity, cancer, cardiovascular disease, hypertension, stroke, cognitive impairment, and early mortality [18, 19, 24, 26, 28, 30, 33, 37, 41]. Therefore, it is important to identify and define "optimal sleep" and discover how deviation from this optimum can affect the risk of developing various diseases. However, this optimum may differ between people depending on their chronotype and other factors. Of the many health outcomes associated with sleep durations outside the recommendation of 7-8 hours, this dissertation examined three outcomes: hypertension, stroke, and mortality. In each of these aims, there was a focus on examining how the relationship between sleep duration and the outcome could differ by factors such as age, sex, ethnicity, BMI, hypertension status, and diabetes status. This investigation adds significant value to this dissertation, as there are very few published studies that have attempted these strata-specific analysis, especially by ethnicity.

This dissertation used data obtained from the MEC, a large prospective study of middle-aged and elderly adults. There were several advantages to using this data source, such as a large sample size, long follow-up, extensive information on various demographic, anthropometric, dietary, lifestyle, and medical factors, and the ethnic diversity in the population. Each study had its unique set of limitations, but findings from this dissertation project are valuable and has many public health implications.

5.2 Summary of the aims

In this dissertation, the author aimed to investigate the role sleep plays in various disease etiology. The first aim examined the association between sleep duration and hypertension prevalence, and how this association differed by age, sex, ethnicity, and BMI. The hypothesis was that both short and long sleep durations, compared to 7 hours, would increase the risk of hypertension as seen in previous literature [31-33, 82]. The hypothesis was supported, and the main finding in this study is that ≤5 hours and ≥10 hours of sleep is associated with a 7% and 8% increase in hypertension prevalence. Examination of prevalence differences revealed that sleep durations of ≤5, 9, and ≥10 hours was theoretically attributed to 31, 23, and 42 excess cases of prevalent hypertension. The association between sleep duration and incident hypertension was also examined, but no association was found. The association was also consistent across age, sex, ethnicity, and BMI groups, suggesting that these factors are not effect modifiers of the sleep-hypertension relationship.

The second aim examined the association between sleep duration and incident stroke, and this association was examined by age, sex, ethnicity, BMI, hypertension, and diabetes subgroups. Previous studies examining the association between sleep duration and stroke have found a U- or J-shaped association [34, 35], so similar findings were expected in this study. As hypothesized, both short and long sleep durations were associated with increased risk for incident stroke. Those reporting ≤5 and ≥10 hours of sleep experienced a 13% and 39% increased risk of stroke, respectively. Differences in the association was not seen across sex. There was a higher risk of stroke among participants with no histories of hypertension or diabetes in some sleep categories, compared to those who reported to have one of these conditions. Comparison of excess cases

across these categories revealed that this difference was likely due to lower baseline risk of stroke in participants without hypertension or diabetes.

The third aim examined the association between sleep duration and mortality. It was hypothesized that both sleep deprivation and excess sleep would be risk factors for all-cause, cardiovascular, and stroke mortality. Compared to participants reporting 7 hours of sleep, those reporting ≤5, 9, and ≥10 hours were at a 12%, 13%, and 39% increased risk of all-cause mortality. These same sleep groups were also associated with an increased cardiovascular and stroke mortality. Exclusion of cases occurring early in the follow-up did not change the results. We also found that age and BMI may be potential effect modifiers of the association. A synergistic association between sleep duration and BMI was reported, where combinations of long sleep duration and being underweight or obese increased the risk of mortality, compared to participants with a healthy BMI and reporting 7 hours of sleep. Synergistic associations between sleep duration and hypertension and diabetes were also found, in which long sleepers with these conditions were at highest risk of death.

5.3 Proposed Mechanisms

This dissertation aimed to uncover the role of sleep duration on human health by studying three different important health outcomes. The intent of the chapters was to build upon each other, that is, findings from one study would help explain the findings of another. Figure 8 shows the conceptual framework behind this dissertation work. The first aim investigated sleep duration as a risk factor for hypertension, which is arguably one of the most important risk factors for diabetes, cardiovascular disease, and early mortality. Preventing the onset of this "silent killer" has been a global public health priority, and there have been a lot of interest in studying

behavioral risk factors for hypertension. As shown in Figure 8, there are biologically plausible mechanisms that link sleep duration with hypertension, such as overactivity of the sympathetic nervous system [119], atherosclerosis [122], higher cortisol and cholesterol levels [123], decreased glucose tolerance [124], and inflammation [125]. Findings in Chapter 2 suggested a weak association between sleep duration and prevalent hypertension and no association with incident hypertension. These findings were unexpected and may be partially due to the methodology used to ascertain hypertension cases. Hypertension is already a condition that is underdiagnosed, and this issue may have been amplified by the self-reported nature of case ascertainment. Hypertension prevalence also increases significantly with age, so it is likely that the study underestimated the number of cases. This may have caused an inadequate exclusion of participants with prevalent hypertension in the incidence analysis. This misclassification may also have affected the findings from Chapter 3, where an independent association between sleep duration and stroke was found even after adjustments for baseline hypertension. However, it is much more likely that the link between sleep duration and stroke is explained by more than one pathway, and not a single pathway mediated by hypertension. Finally, the relationship between sleep duration and mortality is also hypothesized to be involve multiple pathways that are mediated by a variety of demographic, anthropometric, and behavioral risk factors.

In summary, this complex interactions between sleep behaviors and other sociodemographic and behavioral risk factors make it difficult to translate findings from this dissertation into public health recommendations. Individual requirements for sleep likely differ from person to person and combined with the complexity of the underlying mechanisms involved, it is dangerous to assume that sleeping optimal sleep durations alone would directly translate to better health.

5.4 Future Directions

Despite its limitations, this dissertation was able to establish sleep duration as a risk factor for hypertension, stroke, and mortality, independent of sociodemographic and behavioral factors. Based on learned lessons working on this project, the author will present several suggestions for improving and designing future sleep studies. In this dissertation, sleep duration was self-reported from a questionnaire, inquiring on the "average sleep duration (over a 24-hour period) in the past year". This question could be interpreted in numerous ways and makes it impossible to distinguish napping and nocturnal sleep. It is also unlikely for this one-time measure to be adequate predictors of disease, so future studies should also consider sleep trajectories over a longer period. This approach has already been implemented in several studies. For example, in the Whitehall II cohort study, sleep durations were measured once at baseline and once again 4 years later, and this "change in sleep" was used as the sleep exposure [194]. Compared to participants who did not change their sleep behavior, those who decreased their sleep from 6, 7, or 8 hours at baseline and those who increased their sleep duration from 7 or 8 hours were at a higher risk of all-cause and cardiovascular mortality. In a recent Chinese study, compared to participants who reported 7 to 8 hours of sleep over a 4-year period, participants who had decreased their sleep and those who remained short sleepers were at a higher risk of mortality a few years later [233]. This methodology could be implemented with the MEC, as there are also the same sleep questions in Qx3 (2003-2008) and Qx4 (2008-2012).

Contrary to the point made in the previous paragraph, it is also equally important for sleep behaviors to be measured using multiple sleep measures. The majority of studies focus on a single sleep variable, such as sleep duration, snoring, or insomnia. One suggestion is for more studies to utilize sleep indices, such as the Pittsburg Sleep Quality Index (PSQI). The PSQI is a

questionnaire that determines the sleep quality of an individual by taking into account subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction [234]. Measuring sleep quality with validated instruments such as the PSQI once every few years may be the best way to capture sleep data in large population-based studies.

In conclusion, the evolution of sleep research is contingent on improvements in measuring sleep. Experimental sleep studies conducted in laboratories are currently the gold standard in measuring sleep disorders, but these cannot be conducted in large population-based studies, and it also is unable to capture habitual sleep duration. Therefore, subjective sleep measurement strategies also need to evolve. Finally, although it was the intent of this dissertation to identify independent associations between sleep duration and the outcomes, it is important to consider that the physiological changes that occur due to various sleep behaviors are also affected by many other factors.

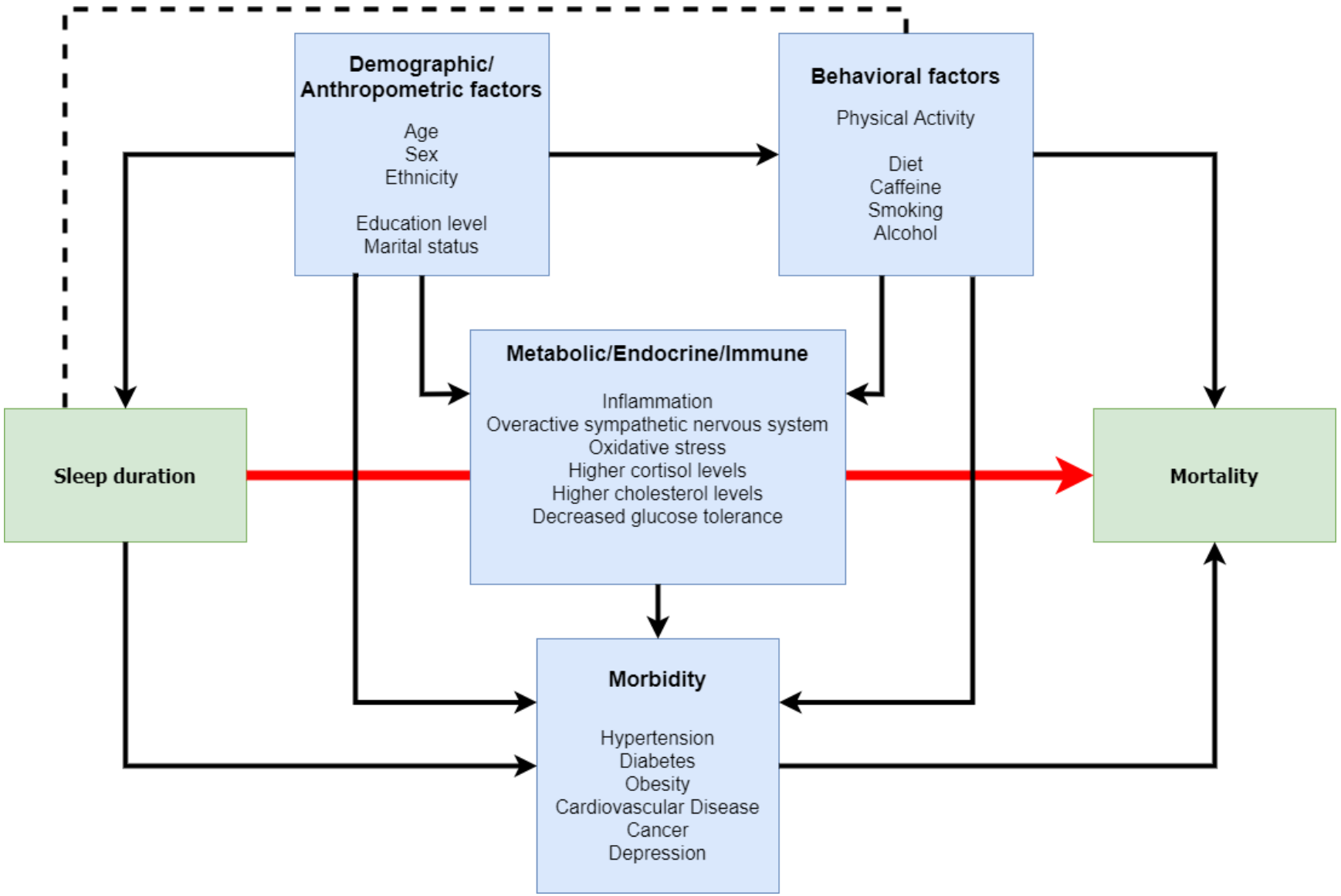

Figure 8. Conceptual framework linking sleep duration and human health.

REFERENCES

1. Bin, Y.S., N.S. Marshall, and N. Glozier, *Sleeping at the limits: the changing prevalence of short and long sleep durations in 10 countries.* American Journal of Epidemiology, 2013. **177**(8): p. 826-833.
2. Basner, M. and D.F. Dinges, *Sleep duration in the United States 2003–2016: first signs of success in the fight against sleep deficiency?* Sleep (New York, N.Y.), 2018. **41**(4): p. 1.
3. Ford, E.S., T.J. Cunningham, and J.B. Croft, *Trends in Self-Reported Sleep Duration among US Adults from 1985 to 2012.* Sleep, 2015. **38**(5): p. 829-832.
4. Center for Disease Control and Prevention. *Sleep and Sleep Disorders–Data and Statistics*. 2020 [cited 2020 1/12/2020]; Available from: https://www.cdc.gov/sleep/data_statistics.html.
5. Robbins, R., et al., *Four-Year Trends in Sleep Duration and Quality: A Longitudinal Study Using Data from a Commercially Available Sleep Tracker.* Journal of medical Internet research, 2020. **22**(2): p. e14735-e14735.
6. Khubchandani, J. and J.H. Price, *Short Sleep Duration in Working American Adults, 2010-2018.* Journal of community health, 2020. **45**(2): p. 219-227.
7. Malik, S.W. and J. Kaplan, *Sleep Deprivation.* Primary care, 2005. **32**(2): p. 475-490.
8. Chatzitheochari, S. and S. Arber, *Lack of sleep, work and the long hours culture: evidence from the UK Time Use Survey.* Work, employment and society, 2009. **23**(1): p. 30-48.
9. Bliwise, D.L., *Historical change in the report of daytime fatigue.* Sleep, 1996. **19**(6): p. 462-464.
10. Basner, M., et al., *American time use survey: sleep time and its relationship to waking activities.* Sleep, 2007. **30**(9): p. 1085-1095.
11. Cain, N. and M. Gradisar, *Electronic media use and sleep in school-aged children and adolescents: A review.* Sleep medicine, 2010. **11**(8): p. 735-742.
12. Colten, H.R. and B.M. Altevogt, *Sleep disorders and sleep deprivation : an unmet public health problem*, ed. H.R. Colten and B.M. Altevogt. 2006, Washington, DC: Institute of Medicine.
13. Ayas, N.T., et al., *A prospective study of self-reported sleep duration and incident diabetes in women.* Diabetes Care, 2003. **26**(2): p. 380.
14. Gottlieb, D., et al., *Association of Sleep Time With Diabetes Mellitus and Impaired Glucose Tolerance.* Archives of Internal Medicine, 2005. **165**(8): p. 863-867.
15. Stranges, S., et al., *Correlates of Short and Long Sleep Duration: A Cross-Cultural Comparison Between the United Kingdom and the United States.* American Journal of Epidemiology, 2008. **168**(12): p. 1353-64.
16. Spiegel, K., et al., *Effects of poor and short sleep on glucose metabolism and obesity risk.* Nature Reviews Endocrinology, 2009. **5**(5): p. 253.
17. Cappuccio, F., et al., *Quantity and Quality of Sleep and Incidence of Type 2 Diabetes.* Diabetes Care, 2010. **33**(2): p. 414-420.
18. Shan, Z., et al., *Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies.* Diabetes care, 2015. **38**(3): p. 529-537.
19. Itani, O., et al., *Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression.* Sleep medicine, 2017. **32**: p. 246-256.

20. Miller, M. and F. Cappuccio, *Inflammation, Sleep, Obesity and Cardiovascular Disease.* Current Vascular Pharmacology, 2007. **5**(2): p. 93-102.
21. Wu, Y., L. Zhai, and D. Zhang, *Sleep duration and obesity among adults: a meta-analysis of prospective studies.* Sleep medicine, 2014. **92**(1): p. 1456–1462.
22. Wu, Y., et al., *Short sleep duration and obesity among children: A systematic review and meta-analysis of prospective studies.* Obesity research & clinical practice, 2017. **11**(2): p. 140-150.
23. Miller, M.A., et al., *Sleep duration and incidence of obesity in infants, children, and adolescents: a systematic review and meta-analysis of prospective studies.* Sleep, 2018. **41**(4): p. 1-19.
24. Liu, W., et al., *Long sleep duration predicts a higher risk of obesity in adults: a meta-analysis of prospective cohort studies.* Journal of Public Health, 2019. **41**(2): p. e158-e168.
25. Lu, Y., et al., *Association between Sleep Duration and Cancer Risk: A Meta-Analysis of Prospective Cohort Studies.* PLoS ONE, 2013. **8**(9): p. e74723.
26. Chen, Y., et al., *Sleep duration and the risk of cancer: a systematic review and meta-analysis including dose–response relationship.* BMC Cancer, 2018. **18**(1): p. 1149.
27. Li, Y., et al., *Association between total sleep time and all cancer mortality: non-linear dose-response meta-analysis of cohort studies.* Sleep medicine, 2019. **60**: p. 211-218.
28. Cappuccio, F.P., et al., *Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies.* European Heart Journal, 2011. **32**(12): p. 1484-1492.
29. Kim, Y., et al., *Insufficient and excessive amounts of sleep increase the risk of premature death from cardiovascular and other diseases: The Multiethnic Cohort Study.* Preventive medicine, 2013. **57**(4): p. 377-385.
30. Kawachi, T., et al., *Sleep Duration and the Risk of Mortality From Stroke in Japan: The Takayama Cohort Study.* Journal of Epidemiology, 2016. **26**(3): p. 123-130.
31. Gottlieb, D.J., et al., *Association of usual sleep duration with hypertension: the Sleep Heart Health Study.* Sleep, 2006. **29**(8): p. 1009-1014.
32. Gangwisch, E.J., et al., *Short Sleep Duration as a Risk Factor for Hypertension: Analyses of the First National Health and Nutrition Examination Survey.* Hypertension, 2006. **47**(5): p. 833-839.
33. Knutson, K.L., et al., *Association Between Sleep and Blood Pressure in Midlife: The CARDIA Sleep Study.* Archives of internal medicine, 2009. **169**(11): p. 1055-1061.
34. von Ruesten, A., et al., *Association of Sleep Duration with Chronic Diseases in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study.* PLoS ONE, 2012. **7**(1): p. e30972.
35. Leng, Y.P., et al., *Sleep duration and risk of fatal and nonfatal stroke: A prospective study and meta-analysis.* Neurology, 2015. **84**(11): p. 1072-1079.
36. Yin, J., et al., *Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies.* Journal of American Heart Association, 2017. **6**(9): p. e005947.
37. Hye Jin, J., et al., *Association between quality and duration of sleep and subjective cognitive decline: a cross-sectional study in South Korea.* Scientific reports, 2021. **11**(1): p. 16989-16989.

38. Winer, J.R., et al., *Association of Short and Long Sleep Duration With Amyloid-β Burden and Cognition in Aging.* JAMA Neurology, 2021.
39. Wu, J., et al., *Prospective associations between change in sleep duration and cognitive impairment: Findings from the Singapore Chinese Health Study.* Journal of affective disorders, 2021. **281**: p. 125-130.
40. Xiao, Q., et al., *Sleep Duration and Total and Cause-Specific Mortality in a Large US Cohort: Interrelationships With Physical Activity, Sedentary Behavior, and Body Mass Index.* American Journal of Epidemiology, 2014. **180**(10): p. 997-1006.
41. Cai, H., et al., *Sleep duration and mortality: a prospective study of 113,138 middle-aged and elderly Chinese men and women.* Sleep, 2015. **38**(4): p. 529-536.
42. Svensson, T., et al., *The association between habitual sleep duration and mortality according to sex and age: the Japan Public Health Center-based Prospective Study.* Journal of epidemiology, 2020.
43. Santoso, A.M.M., et al., *Prevalence of sleep disturbances among head and neck cancer patients: A systematic review and meta-analysis.* Sleep medicine reviews, 2019. **47**: p. 62-73.
44. Ge, L., et al., *Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies.* Sleep medicine reviews, 2019. **48**: p. 1-12.
45. Shi, T., et al., *Does insomnia predict a high risk of cancer? A systematic review and meta-analysis of cohort studies.* Journal of Sleep Research, 2020. **29**(1): p. e12876.
46. Pincherle, A.P., et al., *Sleep, Preconditioning and Stroke.* Stroke, 2017. **48**(12): p. 3400-3407.
47. Kolonel, L.N., et al., *A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics.* American journal of epidemiology, 2000. **151**(4): p. 346-357.
48. Stram, D.O., et al., *Calibration of the Dietary Questionnaire for a Multiethnic Cohort in Hawaii and Los Angeles.* American Journal of Epidemiology, 2000. **151**(4): p. 358-370.
49. Whelton, P.K., et al., *2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary.* Journal of the American College of Cardiology, 2018. **71**(19): p. 2199-2269.
50. Mills, K.T., et al., *Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries.* Circulation, 2016. **134**(6): p. 441-450.
51. Mills, K.T., A. Stefanescu, and J. He, *The global epidemiology of hypertension.* Nature reviews. Nephrology, 2020. **16**(4): p. 223-237.
52. Ritchey, M.D., et al., *Potential need for expanded pharmacologic treatment and lifestyle modification services under the 2017 ACC/AHA Hypertension Guideline.* Journal of Clinical Hypertension, 2018. **20**(10): p. 1377-1391.
53. World Health Organization. *Global Health Risks: Mortality and burden of disease attributable to selected major risks*. 2009 [cited 2020 4/20/2020].
54. National Center for Health Statistics. *CDC WONDER Online Database: Underlying Cause of Death, 1999–2018*. 2020 [cited 2020 4/12/2020]; Available from: https://wonder.cdc.gov/controller/datarequest/D76jsessionid=5D83A183641CB8BCD7FDFADB6DE158F.

55. Kochanek, K.D., et al., *Deaths: Final Data for 2017.* National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 2019. **68**(9): p. 1-77.
56. Rapsomaniki, E., et al., *Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people.* Lancet, 2014. **383**: p. 1899-1911.
57. Sesso, H.D., et al., *Systolic and Diastolic Blood Pressure, Pulse Pressure, and Mean Arterial Pressure as Predictors of Cardiovascular Disease Risk in Men.* Hypertension, 2000. **36**(5): p. 801-807.
58. Rutan, G.H., et al., *Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Factor Intervention Trial.* Circulation, 1988. **77**(3): p. 504-514.
59. Benetos, A., et al., *Prognostic Value of Systolic and Diastolic Blood Pressure in Treated Hypertensive Men.* Archives of internal medicine, 2002. **162**(5): p. 577-581.
60. Dorresteijn, J.A.N., F.L.J. Visseren, and W. Spiering, *Mechanisms linking obesity to hypertension.* Obesity Reviews, 2012. **13**(1): p. 17-26.
61. de Boer, I.H., et al., *Diabetes and Hypertension: A Position Statement by the American Diabetes Association.* Diabetes care, 2017. **40**(9): p. 1273-1284.
62. Fox, C.S., et al., *Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association.* Diabetes care, 2015. **38**(9): p. 1777-1803.
63. Chan, Q., et al., *An Update on Nutrients and Blood Pressure Summary of INTERMAP Study Findings.* Journal of Atherosclerosis and Thrombosis, 2016. **23**(3): p. 276-289.
64. Savica, V., G. Bellinghieri, and J.D. Kopple, *The Effect of Nutrition on Blood Pressure.* Annual Review of Nutrition, 2010. **30**(1): p. 365-401.
65. National Heart Lung and Blood Institute. *DASH Eating Plan*. 2020 [cited 2021 5/28/2021].
66. Sacks, F.M., et al., *Effects on Blood Pressure of Reduced Dietary Sodium and the Dietary Approaches to Stop Hypertension (DASH) Diet.* The New England journal of medicine, 2001. **344**(1): p. 3-10.
67. Saneei, P., et al., *Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: A systematic review and meta-analysis on randomized controlled trials.* Nutrition, metabolism, and cardiovascular diseases, 2014. **24**(12): p. 1253-1261.
68. Sukhato, K., et al., *Efficacy of different dietary patterns on lowering of blood pressure level: an umbrella review.* The American journal of clinical nutrition, 2020. **112**(6): p. 1584-1598.
69. Nowson, C.A., N. Wattanapenpaiboon, and A. Pachett, *Low-sodium Dietary Approaches to Stop Hypertension–type diet including lean red meat lowers blood pressure in postmenopausal women.* Nutrition research (New York, N.Y.), 2009. **29**(1): p. 8-18.
70. Semlitsch, T., et al., *Increasing Physical Activity for the Treatment of Hypertension: A Systematic Review and Meta-Analysis.* Sports Medicine, 2013. **43**(10): p. 1009-1023.
71. Hayashi, T., et al., *Walking to work and the risk for hypertension in men: the Osaka Health Survey.* Annals of internal medicine, 1999. **131**(1): p. 21-26.
72. Luo, W., et al., *Interaction of current alcohol consumption and abdominal obesity on hypertension risk.* Physiology & Behavior, 2013. **122**: p. 182-186.

73. Klatsky, A.L., *Alcohol and Cardiovascular Mortality: Common Sense and Scientific Truth.* Journal of the American College of Cardiology, 2010. **55**(13): p. 1336-1338.
74. Roerecke, M., et al., *Sex-Specific Associations Between Alcohol Consumption and Incidence of Hypertension: A Systematic Review and Meta-Analysis of Cohort Studies.* Journal of the American Heart Association, 2018. **7**(13): p. e008202.
75. Nan, X., et al., *The interactive association between sodium intake, alcohol consumption and hypertension among elderly in northern China: a cross-sectional study.* BMC geriatrics, 2021. **21**(1): p. 135-135.
76. Fagard, R.H., *Smoking amplifies cardiovascular risk in patients with hypertension and diabetes.(SMOKING).* Diabetes Care, 2009. **32**(11): p. S429-S431.
77. Dochi, M., et al., *Smoking as an independent risk factor for hypertension: a 14-year longitudinal study in male Japanese workers.* The Tohoku journal of experimental medicine, 2009. **217**(1): p. 37-43.
78. Bowman, T.S., et al., *A Prospective Study of Cigarette Smoking and Risk of Incident Hypertension in Women.* Journal of the American College of Cardiology, 2007. **50**(21): p. 2085-2092.
79. Jaehne, A., et al., *How smoking affects sleep: A polysomnographical analysis.* Sleep medicine, 2012. **13**(10): p. 1286-1292.
80. Sabanayagam, C. and A. Shankar, *The association between active smoking, smokeless tobacco, second-hand smoke exposure and insufficient sleep.* Sleep medicine, 2011. **12**(1): p. 7-11.
81. Thomas, J.S., et al., *Association of Sleep Characteristics With Nocturnal Hypertension and Nondipping Blood Pressure in the CARDIA Study.* Journal of the American Heart Association, 2020. **9**(7): p. e015062.
82. Wang, Y., et al., *Relationship between Duration of Sleep and Hypertension in Adults: A Meta-Analysis.* Journal of clinical sleep medicine, 2015. **11**(9): p. 1047-1056.
83. Ma, C.C., et al., *Associations of objectively measured sleep characteristics and incident hypertension among police officers: The role of obesity.* Journal of sleep research, 2020: p. e12988.
84. Lopez-Garcia, E., et al., *Self-Reported Sleep Duration and Hypertension in Older Spanish Adults.* Journal of the American Geriatrics Society, 2009. **57**(4): p. 663-668.
85. Van Den Berg, J.F., et al., *Sleep Duration and Hypertension Are Not Associated in the Elderly.* Hypertension, 2007. **50**(3): p. 585-589.
86. Fang, J., et al., *Association of Sleep Duration and Hypertension Among US Adults Varies by Age and Sex.* American journal of hypertension, 2012. **25**(3): p. 335-341.
87. Kim, J. and I. Jo, *Age-Dependent Association Between Sleep Duration and Hypertension in the Adult Korean Population.* American journal of hypertension, 2010. **23**(12): p. 1286-1291.
88. Cappuccio, P.F., et al., *Gender-Specific Associations of Short Sleep Duration With Prevalent and Incident Hypertension: The Whitehall II Study.* Hypertension, 2007. **50**(4): p. 693-700.
89. Guo, X., et al., *Epidemiological evidence for the link between sleep duration and high blood pressure: A systematic review and meta-analysis.* Sleep medicine, 2013. **14**(4): p. 324-332.
90. Han, B., et al., *Sleep and hypertension.* Sleep & breathing, 2020. **24**(1): p. 351-356.

91. Grandner, M., et al., *Sleep Duration and Hypertension: Analysis of > 700,000 Adults by Age and Sex.* Journal of clinical sleep medicine, 2018. **14**(6): p. 1031-1039.
92. Rothman, K.J., *Epidemiology : an introduction*. 2nd ed. ed. 2012, New York, NY: Oxford University Press.
93. Chaput, J.-P., C. Dutil, and H. Sampasa-Kanyinga, *Sleeping hours: what is the ideal number and how does age impact this?* Nature and Science of Sleep, 2018. **10**: p. 421-430.
94. Burgard, S.A. and J.A. Ailshire, *Gender and Time for Sleep among U.S. Adults.* American sociological review, 2013. **78**(1): p. 51-69.
95. Grandner, M.A., et al., *Sleep disparity, race/ethnicity, and socioeconomic position.* Sleep medicine, 2016. **18**: p. 7-18.
96. Patel, N.P., et al., *"Sleep disparity" in the population: poor sleep quality is strongly associated with poverty and ethnicity.* BMC public health, 2010. **10**(1): p. 475.
97. Shigesato, M., et al., *Association between sleep duration and breast cancer incidence: The multiethnic cohort.* International Journal of Cancer, 2020. **146**(3): p. 664-670.
98. Pandit, A.U., et al., *Education, literacy, and health: Mediating effects on hypertension knowledge and control.* Patient education and counseling, 2009. **75**(3): p. 381-385.
99. Taheri, S., et al., *Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index (Leptin, Ghrelin, and Sleep).* PLoS Medicine, 2004. **1**(3): p. e62.
100. Jackson, C.L., et al., *The Relationship between Alcohol Drinking Patterns and Sleep Duration among Black and White Men and Women in the United States.* International journal of environmental research and public health, 2018. **15**(3): p. 557.
101. Chaput, J.-P., et al., *Short sleep duration is associated with greater alcohol consumption in adults.* Appetite, 2012. **59**(3): p. 650-655.
102. Landolt, H., *Caffeine, the circadian clock, and sleep.* Science, 2015. **349**(6254): p. 1289.
103. Landolt, H.-P., et al., *Caffeine Attenuates Waking and Sleep Electroencephalographic Markers of Sleep Homeostasis in Humans.* Neuropsychopharmacology, 2004. **29**(10): p. 1933-1939.
104. Chei, C.-L., et al., *Coffee, tea, caffeine, and risk of hypertension: The Singapore Chinese Health Study*. European Journal of Nutrition, 2018. **57**(4): p. 1333-1342.
105. Mondin, T.C., et al., *Diet quality, dietary patterns and short sleep duration: a cross-sectional population-based study.* European journal of nutrition, 2019. **58**(2): p. 641-651.
106. Almoosawi, S., et al., *Long Sleep Duration and Social Jetlag Are Associated Inversely with a Healthy Dietary Pattern in Adults: Results from the UK National Diet and Nutrition Survey Rolling Programme Y1–4.* Nutrients, 2018. **10**(9): p. 1131.
107. Dashti, H.S., et al., *Short sleep duration and dietary intake: epidemiologic evidence, mechanisms, and health implications.* Advances in nutrition (Bethesda, Md.), 2015. **6**(6): p. 648-659.
108. Takase, H., et al., *Dietary Sodium Consumption Predicts Future Blood Pressure and Incident Hypertension in the Japanese Normotensive General Population.* Journal of the American Heart Association, 2015. **4**(8): p. e001959.
109. Semplonius, T. and T. Willoughby, *Long-Term Links between Physical Activity and Sleep Quality.* Medicine & Science in Sports & Exercise, 2018. **50**(12): p. 2418-2424.

110. Vaz Fragoso, C.A., et al., *Effect of Structured Physical Activity on Sleep–Wake Behaviors in Sedentary Elderly Adults with Mobility Limitations.* Journal of the American Geriatrics Society, 2015. **63**(7): p. 1381-1390.
111. Lambiase, J.M., et al., *Temporal Relationships between Physical Activity and Sleep in Older Women.* Medicine & Science in Sports & Exercise, 2013. **45**(12): p. 2362-2368.
112. McClain, J.J., et al., *Associations between physical activity, sedentary time, sleep duration and daytime sleepiness in US adults.* Preventive medicine, 2014. **66**: p. 68-73.
113. Nymo, S., et al., *Association between habitual sleep duration/quality and appetite markers in individuals with obesity.* Physiology & behavior, 2021. **232**: p. 113345-113345.
114. Simou, E., J. Britton, and J. Leonardi-Bee, *Alcohol and the risk of sleep apnoea: a systematic review and meta-analysis.* Sleep medicine, 2018. **42**: p. 38-46.
115. Liang, H., et al., *Dietary Approaches to Stop Hypertension (DASH) Score and Its Association with Sleep Quality in a National Survey of Middle-Aged and Older Men and Women.* Nutrients, 2020. **12**(5): p. 1510.
116. van Egmond, L., et al., *Association between Healthy Dietary Patterns and Self-Reported Sleep Disturbances in Older Men: The ULSAM Study.* Nutrients, 2019. **11**(5): p. 1029.
117. Frank, S., et al., *Diet and Sleep Physiology: Public Health and Clinical Implications.* Frontiers in neurology, 2017. **8**: p. 393-393.
118. Fung, T.T., et al., *Adherence to a DASH-Style Diet and Risk of Coronary Heart Disease and Stroke in Women.* Archives of internal medicine (1960), 2008. **168**(7): p. 713-720.
119. Dijk, D.-J., *Slow-wave sleep, diabetes, and the sympathetic nervous system.* Proceedings of the National Academy of Sciences of the United States of America, 2008. **105**(4): p. 1107-1108.
120. Calhoun, D.A. and S.M. Harding, *Sleep and hypertension.* Chest, 2010. **138**(2): p. 434-443.
121. Sands, M.R., et al., *Short Sleep Duration Is Associated With Carotid Intima-Media Thickness Among Men in the Coronary Artery Risk Development in Young Adults (CARDIA) Study.* Stroke, 2012. **43**(11): p. 2858-2864.
122. King, C.R., et al., *Short Sleep Duration and Incident Coronary Artery Calcification.* JAMA : the journal of the American Medical Association, 2008. **300**(24): p. 2859-2866.
123. Zhan, Y., R. Chen, and J. Yu, *Sleep duration and abnormal serum lipids: the China Health and Nutrition Survey.* Sleep medicine, 2014. **15**(7): p. 833-839.
124. Spiegel, K., R. Leproult, and E. Van Cauter, *Impact of sleep debt on metabolic and endocrine function.* The Lancet, 1999. **354**(9188): p. 1435-1439.
125. Wilder-Smith, A., et al., *Impact of partial sleep deprivation on immune markers.* Sleep medicine, 2013. **14**(10): p. 1031-1034.
126. Patel, S.R., et al., *Sleep duration and biomarkers of inflammation.* Sleep, 2009. **32**(2): p. 200-204.
127. Abe, T., et al., *Sleep duration is significantly associated with carotid artery atherosclerosis incidence in a Japanese population.* Atherosclerosis, 2011. **217**(2): p. 509-513.
128. Matsubayashi, H., et al., *Long sleep duration and cardiovascular disease: Associations with arterial stiffness and blood pressure variability.* The journal of clinical hypertension (Greenwich, Conn.), 2021. **23**(3): p. 496-503.

129. Najafi, F., et al., *Validity of Self-reported Hypertension and Factors Related to Discordance Between Self-reported and Objectively Measured Hypertension: Evidence From a Cohort Study in Iran.* Journal of preventive medicine and public health, 2019. **52**(2): p. 131-139.
130. Gonçalves, V.S.S., et al., *Accuracy of self-reported hypertension: a systematic review and meta-analysis.* Journal of hypertension, 2018. **36**(5): p. 970-978.
131. Okunowo, O., et al., *Age- and body weight-dependent association between sleep duration and hypertension in US adults: findings from the 2014-2017 National Health Interview Survey.* Sleep health, 2019. **5**(5): p. 509-513.
132. Stranges, S., et al., *A population-based study of reduced sleep duration and hypertension: the strongest association may be in premenopausal women.* Journal of hypertension, 2010. **28**(5): p. 896-902.
133. Lauderdale, S.D., et al., *Self-Reported and Measured Sleep Duration: How Similar Are They?* Epidemiology, 2008. **19**(6): p. 838-845.
134. Signal, L.T., J. Gale, and P.H. Gander, *Sleep measurement in flight crew: comparing actigraphic and subjective estimates to polysomnography.* Aviation, space, and environmental medicine, 2005. **76**(11): p. 1058-1063.
135. Lockley, S.W., D.J. Skene, and J. Arendt, *Comparison between subjective and actigraphic measurement of sleep and sleep rhythms.* Journal of Sleep Research, 1999. **8**(3): p. 175-183.
136. Johnson, W., et al., *Stroke: a global response is needed.* Bulletin of the World Health Organization, 2016. **94**(9): p. 634–634A.
137. Feigin, L.V., A.B. Norrving, and A.G. Mensah, *Global Burden of Stroke.* Circulation Research, 2017. **120**(3): p. 439-448.
138. Virani, S.S., et al., *Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association.* Circulation (New York, N.Y.), 2021. **143**(8): p. e254-e743.
139. Sacco, R.L., et al., *An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association.* Stroke, 2013. **44**(7): p. 2064-2089.
140. Johnston, S.C., S. Mendis, and C.D. Mathers, *Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling.* Lancet neurology, 2009. **8**(4): p. 345-354.
141. Kleindorfer, D.O., et al., *Stroke Incidence Is Decreasing in Whites But Not in Blacks: A Population-Based Estimate of Temporal Trends in Stroke Incidence From the Greater Cincinnati/Northern Kentucky Stroke Study.* Stroke, 2010. **41**(7): p. 1326-1331.
142. Seshadri, S., et al., *The Lifetime Risk of Stroke: Estimates From the Framingham Study.* Stroke, 2006. **37**(2): p. 345-350.
143. Howard, V.J., et al., *Disparities in stroke incidence contributing to disparities in stroke mortality.* Annals of neurology, 2011. **69**(4): p. 619-627.
144. Mozaffarian, D., et al., *Heart Disease and Stroke Statistics—2016 Update: A Report From the American Heart Association.* Circulation, 2016. **133**(4): p. e38-e360.
145. Morgenstern, L.B., et al., *Persistent ischemic stroke disparities despite declining incidence in Mexican Americans.* Annals of Neurology, 2013. **74**(6): p. 778-785.
146. Lackland, T.D., et al., *Factors Influencing the Decline in Stroke Mortality: A Statement From the American Heart Association/American Stroke Association.* Stroke, 2014. **45**(1): p. 315-353.

147. Weiss, J., et al., *Benefits and Harms of Intensive Blood Pressure Treatment in Adults Aged 60 Years or Older: A Systematic Review and Meta-analysis.* Annals of internal medicine, 2017. **166**(6): p. 419-429.
148. Zheng, S. and B. Yao, *Impact of risk factors for recurrence after the first ischemic stroke in adults: A systematic review and meta-analysis.* Journal of clinical neuroscience, 2019. **60**: p. 24-30.
149. Verdecchia, P., et al., *More Versus Less Intensive Blood Pressure–Lowering Strategy: Cumulative Evidence and Trial Sequential Analysis.* Hypertension (Dallas, Tex. 1979), 2016. **68**(3): p. 642-653.
150. Bundy, J.D., et al., *Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-analysis.* JAMA cardiology, 2017. **2**(7): p. 775-781.
151. Khoury, C.J., et al., *Diabetes Mellitus: A Risk Factor for Ischemic Stroke in a Large Biracial Population.* Stroke, 2013. **44**(6): p. 1500-1504.
152. Peters, S.A.E.P., R.R.P. Huxley, and M.P. Woodward, *Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes.* The Lancet (British edition), 2014. **383**(9933): p. 1973-1980.
153. Mitchell, A.B., et al., *Obesity Increases Risk of Ischemic Stroke in Young Adults.* Stroke, 2015. **46**(6): p. 1690-1692.
154. Kizer, J.R., et al., *Measures of Adiposity and Future Risk of Ischemic Stroke and Coronary Heart Disease in Older Men and Women.* American Journal of Epidemiology, 2011. **173**(1): p. 10-25.
155. Hackshaw, A., et al., *Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports.* BMJ, 2018. **360**: p. j5855-j5855.
156. Malek, A.M., et al., *Secondhand Smoke Exposure and Stroke: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study.* American journal of preventive medicine, 2015. **49**(6): p. e89-e97.
157. Peters, S.A.E., R.R. Huxley, and M. Woodward, *Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes.* Stroke (1970), 2013. **44**(10): p. 2821-2828.
158. Yu, L., et al., *Association between physical activity and stroke in a middle-aged and elderly Chinese population.* Medicine (Baltimore), 2018. **97**(51): p. e13568-e13568.
159. Kelley, G.A. and K.S. Kelley, *Leisure Time Physical Activity Reduces the Risk for Stroke in Adults: A Reanalysis of a Meta-Analysis Using the Inverse-Heterogeneity Model.* Stroke research and treatment, 2019. **2019**: p. 8264502-6.
160. Willey, J.Z., et al., *Physical activity and risk of ischemic stroke in the Northern Manhattan Study.* Neurology, 2009. **73**(21): p. 1774-1779.
161. McDonnell, N.M., et al., *Physical Activity Frequency and Risk of Incident Stroke in a National US Study of Blacks and Whites.* Stroke, 2013. **44**(9): p. 2519-2524.
162. Bell, J.E., et al., *Physical Activity and Cardiovascular Disease in African Americans in Atherosclerosis Risk in Communities.* Medicine & Science in Sports & Exercise, 2013. **45**(5): p. 901-907.

163. Micha, R., et al., *Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States.* JAMA : the journal of the American Medical Association, 2017. **317**(9): p. 912-924.
164. O'Donnell, M.J., et al., *Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study.* The Lancet, 2016. **388**(10046): p. 761-775.
165. Estruch, R., et al., *Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts.* The New England journal of medicine, 2018. **378**(25): p. e34(1)-e34(2).
166. Pan, A., et al., *Depression and Risk of Stroke Morbidity and Mortality: A Meta-analysis and Systematic Review.* JAMA : the journal of the American Medical Association, 2011. **306**(11): p. 1241-1249.
167. Hermann, M.D. and L.C. Bassetti, *Role of sleep-disordered breathing and sleep-wake disturbances for stroke and stroke recovery.* Neurology, 2016. **87**(13): p. 1407-1416.
168. Yaggi, H.K., et al., *Obstructive sleep apnea as a risk factor for stroke and death.* The New England journal of medicine, 2005. **353**(19): p. 2034-2041.
169. Li, W., et al., *Sleep duration and risk of stroke events and stroke mortality: A systematic review and meta-analysis of prospective cohort studies.* International Journal of Cardiology, 2016. **223**: p. 870-876.
170. Chen, L.J.-C., et al., *Sleep Duration and Risk of Ischemic Stroke in Postmenopausal Women.* Stroke, 2008. **39**(12): p. 3185-3192.
171. Jike, M., et al., *Long sleep duration and health outcomes: A systematic review, meta-analysis and meta-regression.* Sleep medicine reviews, 2018. **39**: p. 25-36.
172. Amagai, Y., et al., *Sleep duration and incidence of cardiovascular events in a Japanese population: the Jichi Medical School cohort study.* Journal of epidemiology, 2010. **20**(2): p. 106-110.
173. Petrov, E.M., et al., *Sleep duration and risk of incident stroke by age, sex, and race: The REGARDS study.* Neurology, 2018. **91**(18): p. e1702-e1709.
174. Bettger, J.P., et al., *The association between socioeconomic status and disability after stroke: Findings from the Adherence eValuation After Ischemic stroke Longitudinal (AVAIL) registry.(Clinical report).* BMC Public Health, 2014. **14**(1).
175. Feigin, V.L., et al., *Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015.* Circulation Research, 2017. **120**: p. 439-448.
176. Jackson, C.A., C.L.M. Sudlow, and G.D. Mishra, *Education, sex and risk of stroke: a prospective cohort study in New South Wales, Australia.* BMJ Open, 2018. **8**(9): p. e024070.
177. Jimenez, E.M., et al., *Alcohol Consumption and Risk of Stroke in Women.* Stroke, 2012. **43**(4): p. 939-945.
178. Jones, B.S., et al., *Midlife Alcohol Consumption and the Risk of Stroke in the Atherosclerosis Risk in Communities Study.* Stroke, 2015. **46**(11): p. 3124-3130.
179. Kadlecová, P.P., et al., *Alcohol Consumption at Midlife and Risk of Stroke During 43 Years of Follow-Up: Cohort and Twin Analyses.* Stroke, 2015. **46**(3): p. 627-633.
180. Ragab, S., et al., *Caffeine reduces cerebral blood flow in patients recovering from an ischaemic stroke.* Age and Ageing, 2004. **33**(3): p. 299-303.

181. Lee, S.-M., et al., *Caffeine-Containing Medicines Increase the Risk of Hemorrhagic Stroke.* Stroke, 2013. **44**(8): p. 2139-2143.
182. Ding, N.M., et al., *Long-Term Coffee Consumption and Risk of Cardiovascular Disease: A Systematic Review and a Dose–Response Meta-Analysis of Prospective Cohort Studies.* Circulation, 2014. **129**(6): p. 643-659.
183. Hartley, T.R., W.R. Lovallo, and T.L. Whitsett, *Cardiovascular effects of caffeine in men and women.* The American journal of cardiology, 2004. **93**(8): p. 1022-1026.
184. Ge, B. and X. Guo, *Short and Long Sleep Durations are Both Associated with Increased Risk of Stroke: A Meta-Analysis of Observational Studies.* International Journal of Stroke, 2015. **10**(2): p. 177-184.
185. Kato, G.M., et al., *Effects of Sleep Deprivation on Neural Circulatory Control.* Hypertension: Journal of the American Heart Association, 2000. **35**(5): p. 1173-1175.
186. Tochikubo, O., et al., *Effects of Insufficient Sleep on Blood Pressure Monitored by a New Multibiomedical Recorder.* Hypertension, 1996. **27**(6): p. 1318-1324.
187. Li, W., et al., *Is there an association among sleep duration, nap, and stroke? Findings from the China Health and Retirement Longitudinal Study.* Sleep & breathing, 2021. **25**(1): p. 315-323.
188. Jackson, C.A., et al., *Moderate agreement between self-reported stroke and hospital-recorded stroke in two cohorts of Australian women: a validation study.* BMC medical research methodology, 2015. **15**(1): p. 7-7.
189. Reitz, C., et al., *Validity of Self-reported Stroke in Elderly African Americans, Caribbean Hispanics, and Whites.* Archives of neurology (Chicago), 2009. **66**(7): p. 834-840.
190. Magee, C.A., et al., *Investigation of the relationship between sleep duration, all-cause mortality, and preexisting disease.* Sleep medicine, 2013. **14**(7): p. 591-596.
191. Kronholm, E., et al., *Self-reported sleep duration, all-cause mortality, cardiovascular mortality and morbidity in Finland.* Sleep medicine, 2011. **12**(3): p. 215-221.
192. Mesas, A.E., et al., *Sleep Duration and Mortality According to Health Status in Older Adults.* Journal of the American Geriatrics Society, 2010. **58**(10): p. 1870-1877.
193. Ikehara, S., et al., *Association of sleep duration with mortality from cardiovascular disease and other causes for Japanese men and women: the JACC study.* Sleep, 2009. **32**(3): p. 295-301.
194. Ferrie, J.E., et al., *A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort.* Sleep, 2007. **30**(12): p. 1659-1666.
195. Hublin, C., et al., *Sleep and mortality: a population-based 22-year follow-up study.* Sleep, 2007. **30**(10): p. 1245-1253.
196. Lan, T.-Y., et al., *Nighttime sleep, Chinese afternoon nap, and mortality in the elderly.* Sleep, 2007. **30**(9): p. 1105-1110.
197. Shen, X., Y. Wu, and D. Zhang, *Nighttime sleep duration, 24-hour sleep duration and risk of all-cause mortality among adults: a meta-analysis of prospective cohort studies.* Scientific Reports, 2016. **6**(1): p. 21480.
198. Cappuccio, F.P., et al., *Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies.* Sleep, 2010. **33**(5): p. 585-592.
199. Gupta, K., et al., *Sleep duration, baseline cardiovascular risk, inflammation and incident cardiovascular mortality in ambulatory U.S. Adults: National health and nutrition examination survey.* American Journal of Preventive Cardiology, 2021. **8**: p. 100246-100246.

200. Svensson, T., et al., *The Association Between Habitual Sleep Duration and Mortality According to Sex and Age: The Japan Public Health Center-based Prospective Study.* Journal of epidemiology, 2021. **31**(2): p. 109-118.
201. Zhou, T., et al., *Adherence to a healthy sleep pattern is associated with lower risks of all-cause, cardiovascular and cancer-specific mortality.* Journal of internal medicine, 2021(0): p. 1-8.
202. Huang, B.-H., et al., *Sleep and physical activity in relation to all-cause, cardiovascular disease and cancer mortality risk.* British journal of sports medicine, 2021: p. bjsports-2021-104046.
203. Tao, F., et al., *Associations of sleep duration and quality with incident cardiovascular disease, cancer, and mortality: a prospective cohort study of 407,500 UK biobank participants.* Sleep medicine, 2021. **81**: p. 401-409.
204. Pienaar, P.R., et al., *Associations Between Self-Reported Sleep Duration and Mortality in Employed Individuals: Systematic Review and Meta-Analysis.* American journal of health promotion, 2021. **35**(6): p. 853-865.
205. Kakizaki, M., et al., *Long sleep duration and cause-specific mortality according to physical function and self-rated health: the Ohsaki Cohort Study.* Journal of Sleep Research, 2013. **22**(2): p. 209-216.
206. Castro-Costa, E., et al., *Association between sleep duration and all-cause mortality in old age: 9-year follow-up of the Bambui Cohort Study, Brazil.* Journal of Sleep Research, 2011. **20**(2): p. 303-310.
207. Svensson, T., et al., *Association of Sleep Duration With All- and Major-Cause Mortality Among Adults in Japan, China, Singapore, and Korea.* JAMA network open, 2021. **4**(9): p. e2122837-e2122837.
208. Suzuki, E., et al., *Sleep duration, sleep quality and cardiovascular disease mortality among the elderly: A population-based cohort study.* Preventive medicine, 2009. **49**(2): p. 135-141.
209. Luo, Y., Z. Zhang, and D. Gu, *Education and mortality among older adults in China.* Social science & medicine, 2015. **127**: p. 134-142.
210. Arber, S., M. Bote, and R. Meadows, *Gender and socio-economic patterning of self-reported sleep problems in Britain.* Social science & medicine, 2009. **68**(2): p. 281-289.
211. Hislop, J. and S. Arber, *Sleepers Wake! the Gendered Nature of Sleep Disruption among Mid-life Women.* Sociology, 2003. **37**(4): p. 695-711.
212. Rendall, M., et al., *The Protective Effect of Marriage for Survival: A Review and Update.* Demography, 2011. **48**(2): p. 481-506.
213. Staehelin, K., et al., *Marital status, living arrangement and mortality: does the association vary by gender?* Journal of Epidemiology and Community Health, 2012. **66**(7): p. e22.
214. Stanaway, J.D., et al., *Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.* The Lancet, 2018. **392**(10159): p. 1923-1994.
215. Neves, J.S., et al., *Caffeine Consumption and Mortality in Diabetes: An Analysis of NHANES 1999-2010.(Report).* Frontiers in Endocrinology, 2018. **9**: p. 547.

216. Tsujimoto, T., H. Kajio, and T. Sugiyama, *Association Between Caffeine Intake and All-Cause and Cause-Specific Mortality: A Population-Based Prospective Cohort Study.* Mayo Clinic proceedings, 2017. **92**(8): p. 1190-1202.
217. Zaslavsky, O., et al., *Biomarker-calibrated nutrient intake and healthy diet index associations with mortality risks among older and frail women from the Women's Health Initiative.* The American journal of clinical nutrition, 2017. **105**(6): p. 1399-1407.
218. Jones, N.R.V., et al., *Accordance to the Dietary Approaches to Stop Hypertension diet pattern and cardiovascular disease in a British, population-based cohort.* European journal of epidemiology, 2018. **33**(2): p. 235-244.
219. Schoenborn, C.A. and M. Stommel, *Adherence to the 2008 Adult Physical Activity Guidelines and Mortality Risk.* American journal of preventive medicine, 2011. **40**(5): p. 514-521.
220. Hamer, M., et al., *Physical Activity and Cardiovascular Mortality Risk: Possible Protective Mechanisms?* Medicine & Science in Sports & Exercise, 2012. **44**(1): p. 84-88.
221. Troxel, W.M., et al., *Marital Happiness and Sleep Disturbances in a Multi-Ethnic Sample of Middle-Aged Women.* Behavioral sleep medicine, 2009. **7**(1): p. 2-19.
222. Centers for Disease Control and Prevention. *Defining Adult Overweight and Obesity*. [cited 2020 4/23/2020]; Available from: https://www.cdc.gov/obesity/adult/defining.html.
223. Mullington, J.M., et al., *Cardiovascular, Inflammatory, and Metabolic Consequences of Sleep Deprivation.* Progress in cardiovascular diseases, 2009. **51**(4): p. 294-302.
224. Gangwisch, J.E., et al., *Sleep duration associated with mortality in elderly, but not middle-aged, adults in a large US sample.* Sleep, 2008. **31**(8): p. 1087-1096.
225. Dew, A.M., et al., *Healthy Older Adults' Sleep Predicts All-Cause Mortality at 4 to 19 Years of Follow-Up.* Psychosomatic Medicine, 2003. **65**(1): p. 63-73.
226. Haines, A., et al., *The association of hypnotics with incident cardiovascular disease and mortality in older women with sleep disturbances.* Sleep medicine, 2021. **83**: p. 304-310.
227. Grandner, M.A. and S.P.A. Drummond, *Who are the long sleepers? Towards an understanding of the mortality relationship.* Sleep medicine reviews, 2007. **11**(5): p. 341-360.
228. Fernandez-Mendoza, J., et al., *Interplay of Objective Sleep Duration and Cardiovascular and Cerebrovascular Diseases on Cause-Specific Mortality.* Journal of the American Heart Association, 2019. **8**(20): p. e013043-e013043.
229. Maskarinec, G., et al., *Sleep duration and incidence of type 2 diabetes: the Multiethnic Cohort.* Sleep health, 2018. **4**(1): p. 27-32.
230. Wang, Y., et al., *Association between sleep duration and mortality risk among adults with type 2 diabetes: a prospective cohort study.* Diabetologia, 2020. **63**(11): p. 2292-2304.
231. Schantz, M., J.C. Ong, and K.L. Knutson, *Associations between sleep disturbances, diabetes and mortality in the UK Biobank cohort: A prospective population-based study.* Journal of sleep research, 2021: p. e13392-e13392.
232. Su, F., et al., *Associations of shift work and night work with risk of all-cause, cardiovascular and cancer mortality: a meta-analysis of cohort studies.* Sleep medicine, 2021. **86**: p. 90-98.
233. Wang, Y.-H., et al., *Association of Longitudinal Patterns of Habitual Sleep Duration With Risk of Cardiovascular Events and All-Cause Mortality.* JAMA network open, 2020. **3**(5): p. e205246-e205246.

234. Buysse, D.J., et al., *The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research.* Psychiatry research, 1989. **28**(2): p. 193-213.