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Sleep and Markers of Cardiovascular Disease Risk in Elderly Alzheimer's Caregivers

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Public Health (Health Behavior)

by

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The Dissertation of Jennifer Schwartz is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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PUBLICATIONS

1. Schwartz J, Allison MA, Ancoli-Israel S, Hovell MF, Patterson R, Natarajan L, Marshall S, Grant I. Sleep, Type 2 Diabetes, Dyslipidemia, and Hypertension in Elderly Alzheimer's Caregivers. *Under review at the Journal of Applied Gerontology.*
2. Schwartz J, Allison MA, Ancoli-Israel S, Hovell MF, Patterson R, Natarajan L, Marshall S, Grant I. Nighttime Sleep Duration and Efficiency Associated with Plasma Catecholamine Concentrations in Elderly Alzheimer's Caregivers. *Under review at Psychoneuroendocrinology.*
3. Schwartz J, Allison MA, Ancoli-Israel S, Hovell MF, Patterson R, Natarajan L, Marshall S, Grant I. Napping and Less Disturbed Sleep Associated with Reduced Carotid Intima-Media Thickness in Elderly Alzheimer's Caregivers. *Under review at SLEEP*.
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ABSTRACT OF THE DISSERTATION

Sleep and Markers of Cardiovascular Disease Risk in Elderly Alzheimer's Caregivers

by

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Doctor of Philosophy in Public Health (Health Behavior)

University of California, San Diego, 2012
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Background: Sleep has been shown to be shorter and more disturbed in Alzheimer's caregivers compared to non-caregivers, presumably due to challenges associated with caregiving. Caring for a spouse with Alzheimer's disease has also been associated with increased risk for cardiovascular disease (CVD) morbidity and mortality. The increased risk of CVD may be due to the effect that insufficient sleep (disrupted sleep or inadequate sleep duration) has on numerous physiologic processes that can stress the cardiovascular system.

Objectives: This dissertation aimed to (1) assess associations of both sleep duration and efficiency with prevalence of the traditional CVD risk factors of type 2 diabetes, dyslipidemia, and hypertension; (2) investigate whether both sleep duration and efficiency were associated with morning plasma catecholamine concentrations; and (3) determine the associations of both sleep duration and disturbance with carotid intima-media thickness (CIMT) in a sample of community-dwelling elderly Alzheimer's caregivers.

Methods: Participants were 126 caregivers for spouses with Alzheimer's disease who underwent sleep assessment by wrist actigraphy for 72 consecutive hours. Sleep

data were averaged across the 3 days/nights; nighttime sleep and daytime napping were computed. Morning fasting blood samples were collected to determine measures of blood lipids, glucose, and catecholamines (dopamine, epinephrine and norepinephrine); the average of three resting blood pressure measurements was used to estimate mean resting blood pressure; and carotid artery ultrasound was used to measure CIMT. All collections, measurements and assessments were conducted in participants' homes.

Results: Analyses indicate that in an elderly sample of Alzheimer's caregivers, sleep parameters were not significantly associated with prevalent type 2 diabetes, dyslipidemia, or hypertension. However, greater nighttime sleep efficiency and duration were associated with increased morning plasma catecholamine concentrations in this sample of elderly Alzheimer's caregivers. In addition, shorter naps and more disturbed nighttime sleep were associated with increased CIMT.

Conclusions: While findings presented suggest that sleep was not significantly associated with prevalent metabolic conditions, sufficient nighttime sleep and/or napping were associated with increased morning plasma catecholamine concentrations and reduced subclinical carotid atherosclerosis in a sample of elderly Alzheimer's caregivers. These analyses contribute to understanding associations between sleep and markers of cardiovascular disease risk in elderly caregivers. Further research on elderly adults with non-invasive, objective sleep measures is recommended.

CHAPTER 1: Introduction

Background and Significance

Sleep is integral to the maintenance of several physiologic processes such as metabolic, endocrine, autonomic nervous system and cardiovascular functioning.[1-5] Spouses of Alzheimer's patients may experience frequent awakenings during sleep in part due to challenges associated with caregiving.[6] Indeed, caregivers have been found to experience more disrupted sleep with about two-thirds of the 10 million Alzheimer's caregivers in the United States reporting routine sleep disturbance. At the same time, this group is at increased risk for cardiovascular disease (CVD) and death compared to non-caregivers.[6-9] This increased risk of CVD could be partially due to the effect of insufficient sleep on numerous physiologic processes that can stress the cardiovascular system.[10, 11,7] In fact, chronically inadequate sleep has been shown to be an independent predictor of risk for CVD and all-cause mortality.[12, 13]

Although the underlying mechanisms of the adverse effects of insufficient sleep on cardiovascular health are not completely understood, numerous hypotheses have been proposed. For example, insufficient sleep, whether caused by disrupted sleep or inadequate sleep duration, may: 1) mediate fluctuations in neuropeptide levels that regulate appetite (e.g. leptin and ghrelin), thereby leading to increased caloric consumption and weight gain;[14] 2) alter sympathoadrenal medullary (SAM) activity;[15-18] 3) lead to decreased cerebral glucose utilization, which may increase risk of insulin resistance;[19] 4) lead to fatigue, which results in reduced physical activity and energy expenditure, and potential weight gain;[20, 21] and 5) cause elevated inflammatory and coagulation markers, leading to higher risk for development and more rapid

progression of atherosclerosis, which can be represented by carotid intima-media thickness (CIMT).[18, 22-25] As such, insufficient sleep may lead to physiologic perturbations that increase the risk of type 2 diabetes, dyslipidemia, hypertension, and subclinical atherosclerosis (CIMT), all of which predispose individuals to future cardiovascular disease.[26-28]

Sleep and Metabolic Conditions

Insufficient nighttime sleep and napping have been associated with both prevalence and incidence of type 2 diabetes.[29-36] Nonetheless, the health effects of napping are not well understood, as literature regarding daytime sleep in older adults is conflicting.[37, 38] For example, data from several studies indicated that napping was associated with increased risk for CVD-related mortality, while others indicated that napping decreases risk of CVD.[39-42] Evidence regarding associations of sleep with blood pressure, risk of hypertension, and serum lipid-lipoprotein levels in older adults varies.[43-51] Researchers have hypothesized that effects of sleep on blood pressure and serum lipids and lipoproteins may become less evident with age.[45, 47, 52-54]

Sleep and Catecholamines

Plasma dopamine, epinephrine, and norepinephrine (catecholamines released from the adrenal medulla and/or sympathetic neurons that regulate the cardiovascular system and are often used to reflect SAM activity) have heterogeneous actions that depend on the target body tissue type. SAM hyperactivity is thought to promote pathologic processes related to the initiation and progression of vascular and cardiac diseases, yet insufficient amounts of plasma dopamine are hypothesized to increase risk of CVD.[15, 18, 55, 56] Sleep curtailment and/or inefficient sleep have been associated with

altered concentrations of norepinephrine and epinephrine.[17, 18, 57-59] However, findings from these studies are inconsistent, and none have examined associations between sleep and plasma dopamine.[60, 61]

Sleep and Subclinical Atherosclerosis

Researchers hypothesize that insufficient sleep hastens atherosclerotic progression by increasing inflammation, coagulation and SAM activity, and reducing glucose tolerance, which in turn may lead to increased arterial intima-media thickening and risk for CVD events.[7, 11, 18, 22-25] CIMT, a surrogate marker of atherosclerosis and independent predictor of future CVD and events,[62-67] increases with accumulation of lipids, smooth muscle cells, and inflammatory infiltrate.[68] Greater CIMT is associated with CVD risk factors such as increasing age, body mass index (BMI) and cholesterol levels, as well as higher prevalence of diabetes, hypertension, and smoking.[68] The few studies that examined the association between sleep and subclinical carotid atherosclerosis are limited and conflicting.[69, 70]

Objectives

Figure 1.1 (page 8) illustrates hypothesized pathways connecting insufficient nighttime sleep and napping to the outcomes examined in the three manuscripts, thereby demonstrating the relationships between these outcomes of interest. While evidence supporting a link between insufficient sleep and CVD is accumulating, studies on associations of objectively measured sleep with metabolic conditions, plasma catecholamine concentrations, and subclinical atherosclerosis in older adults are limited, often conflicting, and vary widely in terms of research methods and participant characteristics.[25, 58, 71-73] Data on these associations in elderly caregivers are even more

limited, while this group generally experiences sleep difficulties, thus providing greater opportunity for sleep to impact health.[73] Therefore, this dissertation seeks to better understand the relationships between sleep and the identified markers of CVD risk in community-dwelling elderly Alzheimer's caregivers with the following objectives:

1. Assess associations of non-invasive, objectively measured habitual sleep duration and efficiency *with* the presence of type 2 diabetes, dyslipidemia, and hypertension in a sample of community-dwelling elderly Alzheimer's caregivers.
2. Investigate whether non-invasive, objectively measured habitual sleep duration and efficiency are associated *with* morning plasma catecholamine concentrations in a sample of community-dwelling elderly Alzheimer's caregivers.
3. Examine associations of non-invasive, objectively measured habitual sleep duration and disturbance *with* carotid intima-media thickness (CIMT) measured by ultrasound in a sample of community-dwelling elderly Alzheimer's caregivers.

Dissertation Outline

The dissertation includes this introductory chapter (Chapter 1), three manuscripts (Chapters 2-4), and a concluding chapter (Chapter 5). The first manuscript (Chapter 2), entitled "Sleep, Type 2 Diabetes, Dyslipidemia and Hypertension in Elderly Alzheimer's Caregivers" assessed associations of objectively measured sleep duration and efficiency with prevalent type 2 diabetes, hypertension, and dyslipidemia. The second manuscript (Chapter 3), entitled "Nighttime Sleep Duration and Efficiency Associated with Plasma Catecholamine Concentrations in Elderly Alzheimer's Caregivers", investigated whether sleep duration and efficiency were associated with morning plasma dopamine, epinephrine, and norepinephrine concentrations, evaluated objectively in the home. The

third manuscript (Chapter 4), entitled "Napping and Less Disturbed Nighttime Sleep Associated with Reduced Carotid Intima-Media Thickness in Elderly Alzheimer's Caregivers" examined associations of objectively measured sleep quantity and disturbance with subclinical atherosclerosis in the carotid arteries from ultrasound imaging. All three studies examined these associations in a cohort of 126 community-dwelling elderly spousal Alzheimer's caregivers who participated in the Alzheimer Caregiver Coping Study. The final chapter provides a discussion of the central and overlapping themes revealed in the three manuscripts, contextualizes these findings within the broader state of knowledge in the field, and suggests directions for future research.

Overview of Research Methods

The Alzheimer Caregiver Coping Study

The data presented in this dissertation originate from the Alzheimer Caregiver Coping Study, which was conducted at the University of California, San Diego (UCSD) to examine the relationships between physiological and psychological stress markers, and health risk factors in spousal Alzheimer's caregivers. Data were collected between 2007 and 2010, and analyses in all three manuscripts were cross-sectional. A brief description of the research methods used in these manuscripts is provided below, but details are described in each chapter.

Participants

Participants were 126 community-dwelling men and women over 55 years of age who were married, living with, and providing continuous in-home care to a spouse diagnosed with Alzheimer's disease. Caregivers were recruited via referrals from the

UCSD Alzheimer's Disease Research Center, community Alzheimer's caregiver support groups, local agencies serving caregivers, recommendations from other participants enrolled in the study, flyers, media advertisements, and senior health fairs. Participants provided written informed consent, and the study was approved by the UCSD Institutional Review Board.

Caregivers were excluded if they had a current diagnosis or treatment for a life-threatening or terminal medical condition that required ongoing care (i.e. advanced CVD, Parkinson's disease, and/or a severe psychiatric disorder), extreme hypertension (>200/120 mm Hg), current or recent (within the past 5 years) treatment for cancer, organ transplantation requiring anti-rejection medication, or use of corticosteroids, β-blocking, and/or anticoagulant medication.

Measures

The following measurements and assessments, other than the objective sleep measures, were administered between 9:00AM and 11:00AM in participants' homes by trained research personnel: 1) a semi-structured interview that gathered information on sociodemographics, medical history, health behaviors (e.g. smoking status), hospitalizations, duration of caregiving, perceived stress, and depressive symptoms and severity; 2) resting blood pressure measured three times (after 5, 10, and 25 minutes of rest in the supine position); 3) carotid artery ultrasound was conducted with the participant lying in the supine position, using an Acuson Cypress Portable Ultrasound Unit with a 5.4-6.6 MHz Acuson 7L3 transducer; and 4) a fasting blood draw that took place within one week of the initial visit after 10 minutes of rest in the supine position. Objective sleep/wake activity was measured with the Actiwatch-Light® (Mini Mitter Co.,

Inc, a Respironics, Inc. Co., Bend, OR), which was worn for 72 consecutive hours (3 consecutive 24-hour periods).

Statistical Analysis

In all three manuscripts, associations between continuous sleep measures, key covariates (e.g. physical activity), and outcomes of interest were first examined using Pearson *r* and t-tests, which identified potential confounders. First, the sleep variables were treated as continuous. To test for other non-linear associations or thresholds, sleep parameters were also modeled categorically (e.g. by tertiles) and by combining sleep parameters into new variables. In these secondary analyses with combined sleep parameters, reference groups were chosen based on current notions about clinically significant cut points of these sleep parameters in elderly adults.[74-76]

Multivariable regression models were used to examine whether sleep parameters were associated with outcomes of interest (separately). In the regression models, covariates were restricted to age, gender, variables showing significant ($p<0.10$) univariate correlations with the exposure variables (sleep parameters) or the outcome variables, and variables selected a-priori as likely related to sleep and the outcome of interest. Three models were created to examine changes in relationships between the sleep parameters and outcomes of interest as related groups of covariates were added. An alpha level of $p<0.05$ (2-tailed) was used to indicate statistical significance, and all statistical analyses were conducted using SPSS version 16.0 or 19.0.

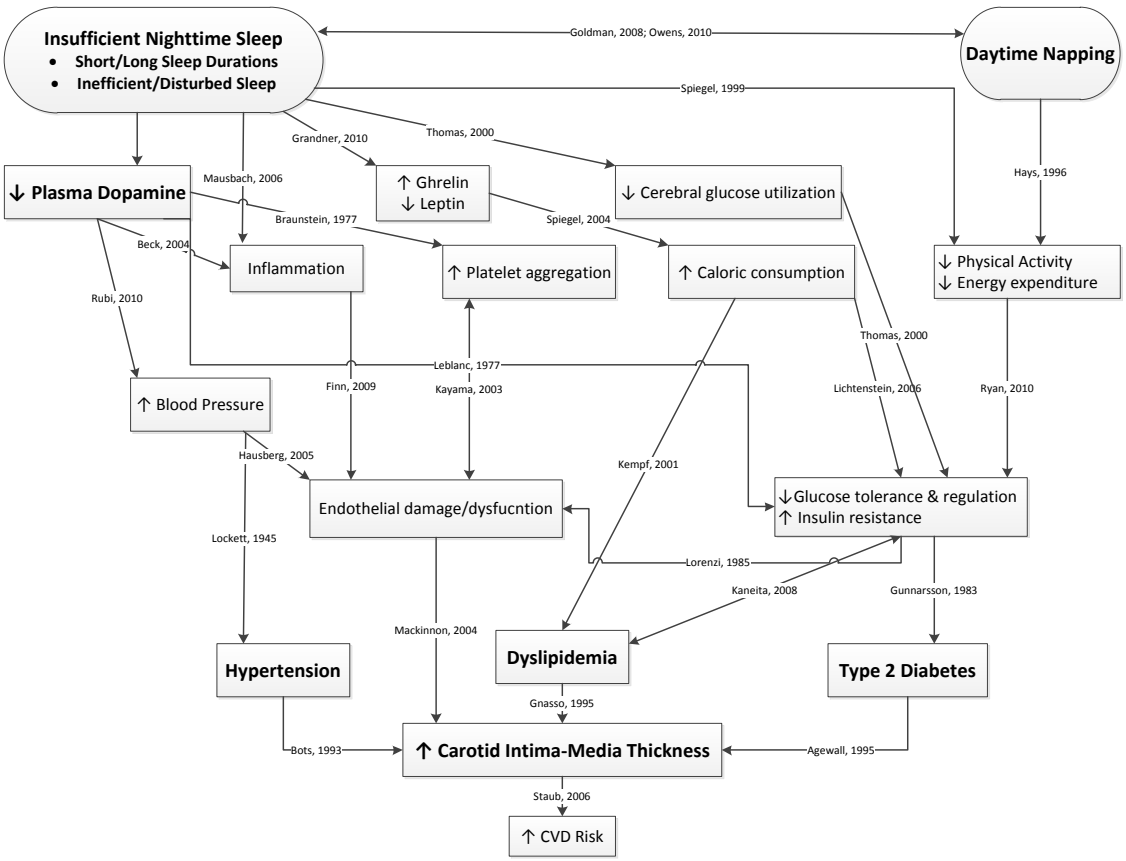

Figure 1.1. Theoretical Model: Hypothesized pathways linking insufficient nighttime sleep and daytime napping with outcomes of interest (**bolded**) and cardiovascular disease risk in elderly Alzheimer's caregivers.

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CHAPTER 2: Sleep, Type 2 Diabetes, Dyslipidemia, and Hypertension in Elderly Alzheimer's Caregivers

Title: Sleep, Type 2 Diabetes, Dyslipidemia and Hypertension in Elderly Alzheimer's Caregivers

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Abstract

Background: Research indicates that very short or long durations of sleep and inefficient sleep, are associated with higher total cholesterol and risk of type 2 diabetes mellitus and hypertension.

Objectives: This study tested the hypothesis that inefficient sleep or short/long sleep durations are associated with an elevated prevalence of type 2 diabetes, dyslipidemia, and hypertension in a community-dwelling sample of elderly Alzheimer's caregivers.

Methods: Participants were 126 caregivers for spouses with Alzheimer's disease who underwent in-home sleep assessment by wrist actigraphy for 72 consecutive hours. Sleep data were averaged across the 3 days/nights; nighttime sleep and daytime napping were computed. Morning fasting blood samples were collected to determine measures of blood lipids and glucose. The average of three resting blood pressure measurements was used to estimate mean resting blood pressure.

Results: Logistic regression models including covariates related to sleep and metabolic regulation indicated that nighttime sleep duration, percent sleep at night, and daytime naps were not significantly associated with odds of having diabetes (OR, 0.92; 95%CI, 0.56-1.53; OR, 0.93; 95%CI, 0.83-1.03; OR, 1.75; 95%CI, 0.74-4.11, respectively), dyslipidemia (OR, 0.83; 95%CI, 0.57-1.20; OR, 0.99; 95%CI, 0.92-1.07; OR, 0.64; 95%CI: 0.33-1.24, respectively), or hypertension (OR, 0.97; 95%CI, 0.62-1.52; OR, 1.02; 95%CI, 0.93-1.11; OR, 1.10; 95%CI, 0.44-2.74, respectively). When categorical and combined sleep parameters were examined, there were no significant associations with any of the metabolic conditions (all $p>0.05$).

Conclusions: The current study suggests that in an elderly sample of Alzheimer's caregivers, nighttime sleep duration, nighttime sleep efficiency and daytime naps are not significantly associated with prevalent type 2 diabetes, dyslipidemia, or hypertension. The small sample size may have limited the power for these analyses. As

several of the associations demonstrated clinically relevant magnitudes of the associations, larger studies to more fully test these hypotheses are warranted.

Introduction

Caregivers are at increased risk for coronary heart disease (CHD), which could be partially due to the effect that inadequate sleep has on numerous physiologic processes, including metabolic regulation.[1-6] Compared to non-caregivers, sleep has been shown to be shorter and more disturbed in Alzheimer's caregivers, presumably due to challenges associated with caregiving.[3, 7, 8] Although the underlying mechanisms of the adverse effects of insufficient sleep on glucose metabolism, blood pressure, and lipid-lipoprotein levels are not completely understood, numerous pathways have been proposed. These include: 1) insufficient nighttime sleep, whether caused by disrupted sleep or by inadequate sleep duration, may lead to increased caloric consumption and weight gain by mediating fluctuations in neuropeptide levels that regulate appetite (e.g. leptin and ghrelin);[9] 2) insufficient sleep may increase sympathetic nervous system activity, which in turn may increase blood pressure;[10, 11] 3) insufficient sleep may lead to decreased cerebral glucose utilization, which may increase risk of insulin resistance;[12] and 4) insufficient sleep leads to tiredness, which results in reduced physical activity and potential weight gain.[13, 14] These physiologic perturbations may lead to increased blood pressure, heightened cholesterol and triglyceride levels, and impaired insulin sensitivity and glucose tolerance; which in turn increase risk of hypertension, dyslipidemia, and type 2 diabetes.

Insufficient nighttime sleep and napping have been associated with the development of type 2 diabetes.[15-19] For example, the National Institutes of Health - AARP Diet and Health Study – a prospective study on older adults – reported that short self-reported nighttime sleep (<5 hours) and longer daytime napping (≥1 hour) were each

associated with increased risk of type 2 diabetes 4-9 years later.[20] Evidence regarding associations of sleep with blood pressure and risk of hypertension in older adults varies.[21-25] For example, Rod et al. reported that sleep disturbances were associated with an increased risk of developing hypertension during 19 years of follow-up.[26] Conversely, analyses from a cross-sectional study indicated that self-reported nighttime sleep duration was not significantly associated with risk of hypertension among adults aged ≥65 years.[21] The few studies that have examined associations between sleep and serum lipids and lipoproteins have also yielded conflicting results.[27-29] A study that objectively measured one night of sleep in young adults (mean age of 30 years) indicated that reduced sleep efficiency was associated with higher total cholesterol.[28] Conversely, a study that used actigraphy to quantify sleep in 983 elderly participants with a mean age of 69 years, reported that nighttime sleep duration and efficiency (defined as less fragmented sleep) were positively associated with total cholesterol and total/HDL cholesterol.[29] Researchers have argued that relationships of sleep with blood pressure and serum lipid-lipoprotein concentrations become less evident with age.[21, 27, 30-32]

Data on objectively measured sleep and metabolic risk factors in older adults are limited and somewhat conflicting.[33-36] Research examining these associations in elderly dementia caregivers is even more limited, yet this group generally experiences frequent sleep difficulties, thereby potentially providing greater opportunity for poor sleep to impact health.[37] The purpose of this cross-sectional analysis was to examine whether sleep duration and efficiency were associated with prevalent diabetes, hypertension, and

dyslipidemia among 126 community-dwelling elderly spousal Alzheimer's caregivers who participated in the Alzheimer Caregiver Coping Study.

Methods

The Alzheimer Caregiver Coping Study

The Alzheimer Caregiver Coping Study was conducted at the University of California, San Diego (UCSD) to examine the relationships between physiological and psychological stress markers, and health risk factors in spousal Alzheimer's caregivers. Data were collected between 2007 and 2010.

Participants were 126 community-dwelling men and women over the age of 55 years who were married, living with, and providing continuous in-home care to a spouse diagnosed with Alzheimer's disease. Caregivers were recruited via referrals from the UCSD Alzheimer's Disease Research Center, community Alzheimer caregiver support groups, local agencies serving caregivers, recommendations from other participants enrolled in the study, flyers, media advertisements, and senior health fairs. Participants provided written informed consent, and the study was approved by the UCSD Institutional Review Board.

Caregivers were excluded if they had a current diagnosis or treatment for a life-threatening or terminal medical condition that required ongoing care (i.e., advanced CVD, Parkinson's disease, and/or a severe psychiatric disorder), extreme hypertension (>200/120 mm Hg), current or recent (within the past 5 years) treatment for cancer, organ transplantation requiring anti-rejection medication, or use of corticosteroids, β-blocking, and/or anticoagulant medication.

Measures

All measurements and assessments, other than objective measures of sleep, were administered between 9:00AM and 11:00AM in participants' homes by trained research personnel.

Sociodemographics, Medical Data, and Past Health History

The research assistant administered a semi-structured interview that gathered information on sociodemographics, medical history, health behaviors (e.g. smoking status) and hospitalizations. History of cardiovascular disease was defined as previous heart attack, heart failure, angina, heart disease, stroke, or transient ischemic attack. Caregivers were asked if they had ever been told by a physician that they had type 2 diabetes, hypertension, dyslipidemia, myocardial infarction or stroke, with answers coded yes/no. Information about cardiovascular medication (i.e., aspirin, angiotensin-converting enzyme inhibitors, and statins) and antidepressant use (i.e., atypicals, selective serotonin reuptake inhibitors, tricyclics, etc.) was obtained via participant report and confirmed by examination of the medication containers.

Smoking status was categorized as current/former smoker vs. never smoker and also measured in terms of years of smoking. Alcohol consumption was quantified in terms of the number of alcoholic drinks consumed per week. Data on height and weight were obtained by participant report, and body mass index (BMI) was calculated as the ratio of self-reported weight in kilograms to height in meters squared. Participants with a BMI > 30 were classified as obese.

Psychological Questionnaires

The semi-structured interview included questionnaires that evaluated duration of caregiving, psychological distress, perceived stress, depressive symptom severity, and

anxiety and depressive symptoms. Duration of caregiving was determined by reported time in years that had elapsed since the spouse was diagnosed with Alzheimer's disease. The 10-item short form of the Center for Epidemiologic Studies Depression Scale (CESD-10) was used to assess depressive symptoms.[38-40] Levels of life stress were assessed with the 4-item Role Overload Scale, a self-report 4-point Likert scale ranging from 1=not at all to 4=completely, which measured the extent to which participants felt overwhelmed by everyday tasks. Lower role overload and CESD-10 scores indicate lower stress and depressive symptoms, respectively. Reliability (Cronbach's alpha) for the 4-item Role Overload Scale has ranged from 0.71 to 0.77 in different samples of elderly caregivers,[41] however, in our sample, the alpha coefficient is 0.82. Cronbach's alpha for the CESD-10 in our sample of caregivers is 0.52.

Objective Sleep Measure

Objective sleep/wake activity was measured with the Actiwatch-Light® (Mini Mitter Co., Inc, a Respironics, Inc. Co., Bend, OR), which was worn for 72 consecutive hours (3 consecutive 24-hour periods) on participants' non-dominant wrist. Actigraphy has been validated in and recommended for use among elderly populations and has been compared favorably with polysomnography, which is deemed the gold standard for sleep assessment.[42, 43] The Actiwatch-Light® uses a piezoelectric linear accelerometer (sensitivity <0.01 g-force) with a sampling rate of 32Hz to measure and record wrist movement. Movement, which was measured as the number of accelerations per minute, was captured via internal motion sensors in the watch. Calculating wrist activity over time allowed for an objective measure of duration and disruption of sleep. The recorded actigraphy data were analyzed using Actiware® sleep and activity monitoring software

(version 5, by Mini Mitter|Respironics/Philips). Sleep diaries completed by participants estimated times the actigraphy watch was removed, bedtimes, and wake times, and were used for editing the actigraphy data.

The following sleep parameters were averaged across the three consecutive 24-hour time periods and selected a priori: 1) total nighttime sleep duration (hours per night spent sleeping from reported bedtime to final uptime); 2) total hours of daytime sleep (nap time), with naps defined as no activity for a minimum of 10 minutes; and 3) percent of time asleep at night between initial sleep onset and final awakening, which was used to denote sleep efficiency.

Outcomes – Type 2 Diabetes, Dyslipidemia and Hypertension

All participant blood samples were collected within one week of the initial visit in a fasting state between 9:00AM and 11:00AM to decrease the impact of diurnal fluctuations, and the first blood draw took place after 10 minutes of rest in the supine position. Total cholesterol, high density lipoproteins, and glucose were measured at the clinical chemistry laboratories at the UCSD Medical Center. Dyslipidemia was defined either by total-to-HDL ratio >5, or by self-report of current use of prescription cholesterol-lowering medications. Type 2 diabetes was defined either by self-report of physician-diagnosed diabetes and current use of antiglycemic medication, or a fasting blood glucose ≥126 mg/dL, as classified by the American Diabetes Association.[44]

Resting blood pressure was measured three times (after 5, 10, and 25 minutes of rest in the supine position) using a non-invasive Microlife BP monitor, model #3AC1-1PC. The average of the three measurements was used to create a composite resting blood pressure estimate. Hypertension was defined either by self-report of physician-

diagnosed hypertension and current use of a prescription antihypertensive, or as a resting diastolic blood pressure or systolic blood pressure ≥90 or ≥140 mmHg, respectively.

Statistical Analysis

Associations between continuous sleep measures, key covariates (e.g. physical activity), and metabolic markers/conditions were first examined using Pearson *r* and t-tests, which identified potential confounders. Univariate analyses were performed to examine sleep parameters and covariates by type 2 diabetes, hypertension, and dyslipidemia status. First, the sleep variables were treated as continuous. To test for other non-linear associations or thresholds, sleep parameters were also modeled categorically by tertiles (nighttime sleep duration tertiles: <6.8, 6.8-7.8, and ≥7.8 hours; daytime sleep duration tertiles: <21, 21-56, and ≥56 minutes; and percent sleep at night tertiles: <85.9%, 85.9-90.2%, and ≥90.2%) and by combining sleep parameters into three new variables: 1) nighttime sleep duration *with* daytime sleep duration; 2) nighttime sleep duration *with* percent sleep at night; and 3) daytime sleep duration *with* percent sleep at night. In these secondary analyses, daytime sleep duration was reported in minutes for ease of interpretation, and in analyses with combined sleep parameters, reference groups were chosen based on current viewpoints about clinically significant cut points of these sleep parameters in elderly adults. Specifically, 7-8 hours of sleep at night, ≥85% sleep at night, and <30 minutes of daytime sleep are generally considered the normal cut-offs for elderly adults, and were therefore used as the reference groups and/or cut points.[42, 45, 46]

Three multivariable logistic regression models were used to determine whether sleep parameters were associated with prevalent type 2 diabetes, dyslipidemia, and

hypertension (separately). To prevent over-fitting in the multiple regression models, covariates were restricted to age, gender, those variables showing significant ($p<0.10$) univariate correlations with the outcome variables (metabolic markers/conditions), and variables selected a-priori likely to be related to metabolic regulation and sleep. These models were created to examine changes in the sleep-metabolic marker relationships as related groups of covariates were added. Covariates adjusted for in the first model (Model 1) included age and gender. The second multivariate model (Model 2) included the covariates from Model 1 plus physical activity, alcohol consumption, smoking status, and BMI. In the third model (Model 3), covariates from Model 2 were included plus Role overload and depression (CESD-10) scores. An alpha level of $p<0.05$ (2-tailed) was used to indicate statistical significance, and all statistical analyses were conducted using SPSS version 16.0 statistical package.

Results

Participant Characteristics

Demographic and health characteristics for the sample of elderly Alzheimer's caregivers are presented in Table 2.1. Caregivers were a mean age of 74 years, primarily women (71%), Caucasian (92%), slightly overweight, and had been providing care for an average of 4.3 years. The majority of caregivers had hypertension (81%) and dyslipidemia (62%), while 19% were found to have Type 2 diabetes, and 20% had a history of cardiovascular disease. On average, caregivers slept 7 hours and 20 minutes and were asleep for 87% of the night, and spent 48 minutes napping.

Continuous Sleep Parameters and Metabolic Conditions

In unadjusted analyses, and compared to caregivers without diabetes, those with diabetes were significantly older, more likely to be Non-Caucasian, had higher BMI, were more likely to have a history of CVD, and had higher Role overload scores and more depressive symptoms on the CESD-10 ($p<0.05$ for all). Similarly, compared to caregivers without hypertension, those with hypertension were significantly older ($p=0.01$). Caregivers with dyslipidemia were not significantly different from those without dyslipidemia (table not shown). As shown in Figures 2.1-2.3, there were no significant differences in napping, nighttime sleep duration or nighttime sleep efficiency between those with or without diabetes, hypertension or dyslipidemia.

Multiple adjusted logistic regression analyses were performed to assess the impact of each sleep parameter on the likelihood that caregivers would have diabetes, hypertension or dyslipidemia. Associations between sleep parameters and each of diabetes, hypertension and dyslipidemia were not statistically significant at the 5% level in any of the models (Table 2.2). Of note, all confidence intervals included "1", yielding results consistent with the null hypothesis of no significant associations between sleep and diabetes, hypertension or dyslipidemia among our Alzheimer's caregivers.

As presented in Table 2.2, when adjusting for covariates in Model 3, for every additional hour of sleep obtained during the day, participants were 1.75 times more likely to have diabetes (OR, 1.75; 95%CI, 0.74-4.11). For each 1% increase in time spent asleep during the night, caregivers were 7% less likely to have diabetes (OR, 0.93; 95%CI, 0.83-1.03). For each additional hour of sleep obtained during the night, caregivers were 8% less likely to have diabetes (OR, 0.92; 95%CI, 0.56-1.53). With regard to dyslipidemia, for every additional hour of sleep obtained during the day,

caregivers were 36% (OR, 0.64; 95%CI, 0.33-1.24) less likely to have dyslipidemia. For every additional hour of sleep obtained at night, caregivers were 17% less likely to have dyslipidemia (OR, 0.83; 95%CI, 0.57-1.20). For every 1% increase in time spent asleep at night, the likelihood of having dyslipidemia decreased by 1% (OR 0.99, 95%CI, 0.92-1.07). With regard to hypertension, for every additional hour of sleep obtained at night, caregivers were 3% (OR, 0.97; 95%CI, 0.62-1.52) less likely to have hypertension. For every additional hour of sleep obtained during the day, caregivers were 10% (OR, 1.10; 95%CI, 0.44-2.74) more likely to have hypertension. Lastly, for every 1% increase in time spent asleep at night, the likelihood of having hypertension increased by 2% (OR 1.02, 95%CI, 0.93-1.11). None of these associations were statistically significant.

Categorical and Combined Sleep Parameters and Metabolic Conditions

Adjusting for age and gender (Model 1) in sleep-tertile analyses (table not shown), there were no clear trends in prevalence of diabetes, dyslipidemia, or hypertension across nighttime sleep duration tertiles (p_{trend}=0.95, p_{trend}=0.40, p_{trend}=0.57, respectively), daytime sleep duration tertiles (p_{trend}=0.27, p_{trend}=0.12, p_{trend}=0.40, respectively), or percent sleep at night tertiles (p_{trend}=0.23, p_{trend}=0.29, p_{trend}=0.78, respectively). Additionally, prevalence of diabetes, dyslipidemia, and hypertension did not significantly differ by nighttime sleep duration tertile (p=0.71, p=0.66, p=0.57, respectively), daytime sleep duration tertile (p=0.38, p=0.19, p=0.69, respectively), or percent sleep at night tertile (p=0.06, p=0.46, p=0.72, respectively).

Associations between the combined sleep variables (nighttime sleep duration *with* daytime sleep duration; nighttime sleep duration *with* percent sleep at night; and daytime sleep duration *with* percent sleep at night) and the three metabolic markers/conditions

were examined using multinomial logistic regression. As shown in Tables 2.3-2.5, presence of diabetes, dyslipidemia, and hypertension did not significantly differ by any of the combined sleep groups in any of the 3 adjusted models (all $p>0.05$).

Discussion

In this sample of community-dwelling elderly Alzheimer's caregivers, we did not find significant associations of nighttime sleep duration, sleep efficiency at night, or daytime naps with prevalence of diabetes, dyslipidemia, or hypertension. Our secondary analyses with categorical and combined sleep parameters also failed to show significant associations. This may be due to the fact that the caregivers in our sample had less disturbed sleep than has been observed in previous studies, were not considered sleep deprived, and variance in the sleep variables was limited.[45, 47] For instance, our caregivers slept 7 hours and 20 minutes at night and were asleep for 87% of the time, while caregivers in a study by Dhruva et al. slept 6 hours and 45 minutes at night and were asleep 83% of the time based on actigraphy data.[48] Access to additional resources (e.g. home help) could be one explanation for why caregivers in our sample had adequate sleep, as their average annual income was $71,020. The fact that the sleep of the caregivers in our sample was within normal limits may explain the lack of significant associations between the sleep and metabolic measures in our study.

Our null findings are inconsistent with most published studies reporting associations between nighttime sleep and diabetes.[19, 20, 49] For example, a meta-analysis of 10 prospective studies indicated that reported short nighttime sleep (≤5-6 hours), long nighttime sleep (>8-9 hours) and difficulty maintaining sleep (assessed by questionnaire) significantly predicted (OR: 1.28, 95%CI: 1.03-1.06; OR: 1.48, 95%CI: 1.13-1.96; and

OR: 1.84, 95%CI: 1.39-2.43, respectively) incident diabetes.[49] In an attempt to compare our data with results from this meta-analysis, we ran exploratory analyses, which indicated that the prevalence of diabetes among caregivers who slept 6-8 hours at night did not significantly differ (OR: 0.83, 95%CI: 0.32-2.15) from the prevalence among caregivers who slept <6 or >8 hours at night. A different cross-sectional study on 70 participants with a mean age of 60 years that used wrist actigraphy for 3 consecutive days reported that reduced sleep efficiency, defined as percent sleep at night, was associated with the presence of diabetes.[50] Alternatively, literature regarding daytime sleep in older adults is conflicting, as several studies have found that napping is associated with an increased risk of diabetes, while others reported that napping decreases risk of CVD.[20, 51-54] For example, a cross-sectional study on community-dwelling adults over age 50 years found significant dose-response relationships of napping frequency and duration with increased prevalence of type 2 diabetes.[55]

Data are conflicting from the limited number of studies that investigated relationships between sleep and dyslipidemia in older adults.[27-29] Our findings of no significant associations between the sleep parameters and dyslipidemia are consistent with those from a cross-sectional study on women over the age of 50 years that found that reported sleep duration was not significantly associated with plasma lipid-lipoprotein concentrations; the authors concluded that the relationship between sleep and serum lipid-lipoprotein concentrations becomes less evident with age.[27] Our findings are inconsistent with studies suggesting that short nighttime sleep is associated with dyslipidemia. For example, a study by Kaneita et al. found that men who reported

sleeping 6-7 hours at night had higher LDL cholesterol levels compared with those who slept ≥8 hours.[56]

None of the sleep parameters were significantly associated with hypertension in our sample of caregivers. These finding are supported by three known studies that reported no significant associations of sleep with blood pressure, and/or risk of hypertension among elderly adults, perhaps supporting the hypothesis that this relationship decreases with age.[21, 30-32] For example, data from a cross-sectional study on participants over the age of 58 years indicated that sleep duration measured by actigraphy was not associated with hypertension.[31]

It is important to note our study used three days/nights of actigraphy to objectively measure sleep, while previous studies that reported significant correlations between sleep and metabolic conditions often based their sleep measurements on one night of polysomnography or self-report.[22, 24, 26, 55, 56] One night of polysomnography may not be representative of habitual sleep, and self-reported sleep measures are less reliable than objective measurements.[23, 57-59] Therefore, additional trials with non-invasive, objectively measured sleep are needed to help elucidate relationships between sleep and metabolic conditions in older adults.

This sample of caregivers had relatively undisturbed sleep, they were not considered sleep deprived, and there was limited variance in the sleep variables.[45, 47] Our results were consistent with the null hypothesis; however, non-rejection of the null is not necessarily confirmation of it. In particular, the small sample size may have limited the power of the study. For example, given the wide confidence interval for the association between napping and diabetes in model 3 (95%CI: 0.74-4.11), we may have been

underpowered to detect an odds ratio as high as 4. Alternatively, the tight confidence interval for the association between percent sleep at night and dyslipidemia in model 3 (95%CI: 0.92-1.07) is consistent with the null hypothesis. Therefore, there may have been inadequate power to detect significant associations between napping and type 2 diabetes, as only 23 caregivers had diabetes, but adequate power to detect associations between percent sleep at night and dyslipidemia, as 74 caregivers had dyslipidemia. Nevertheless, the majority of the associations between the sleep parameters and metabolic conditions were in the hypothesized direction, and with a larger sample size some of the associations that were close to significance may in fact be significant.

Conclusions

Limited physical activity, poor diet, smoking, and excessive alcohol consumption increase risk of type 2 diabetes, dyslipidemia, and hypertension; but insufficient sleep, a modifiable health behavior, could be an additional risk factor.[20, 23, 60, 61] A more complete theoretical model of the etiology of type 2 diabetes, dyslipidemia, and hypertension in older adults that includes sleep ought to be considered in future studies. If the hypothesized relationships are found to exist, this model could offer valid, directionally-oriented physiologic mechanisms that link sleep to these metabolic conditions. Understanding these mechanisms that connect insufficient nighttime sleep and daytime naps to metabolic regulation has the potential to aid practitioners in the prevention and management of these prevalent and escalating chronic diseases.

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Diabetes, Dyslipidemia, and Hypertension in Elderly Alzheimer's Caregivers. Jennifer Schwartz was the primary author of this manuscript.

Table 2.1. Characteristics of a sample of elderly Alzheimer's caregivers (N=126) in a study of the associations of sleep with type 2 diabetes, dyslipidemia, and hypertension

Age (years), mean (SD)	74.16 (7.98)
Female, n (%)	89 (71.20)
Ethnicity, n (%)	
Caucasian	115 (92.00)
Non-Caucasian	10 (8.00)
Education (years), mean (SD)	15.15 (3.05)
Body mass index (kg/m^2), mean (SD)	26.49 (4.71)
Systolic blood pressure (mmHg), mean (SD)	134.3 (15.3)
Diastolic blood pressure (mmHg), mean (SD)	75.8 (8.6)
Blood glucose (mg/dL), mean (SD)	105.1 (43.7)
History of cardiovascular disease, n (%)[1]	25 (19.84)
Duration of caregiving (years), mean (SD)	4.33 (3.38)
Health Behaviors	
Ever smoker, n (%)	58 (46.03)
Alcohol consumption (drinks/week), mean (SD)	1.40 (1.46)
Meets CDC physical activity recommendation, n (%)[2]	42 (33.30)
Psychological Variables	
Role overload score, mean (SD)	5.18 (3.15)
CESD-10 score, mean (SD)	8.78 (5.81)
Medication Use	
Current use of antidepressants, n (%)	32 (25.40)
Current use of cholesterol-lowering medication, n (%)	57 (45.20)
Current use of high blood pressure medication, n (%)	76 (60.30)
Current use of diabetes medication, n (%)	15 (11.90)
Objective Sleep Variables	
Nighttime sleep duration (hours), mean (SD)	7.32 (1.12)
Daytime sleep duration (hours), mean (SD)	0.79 (0.67)
Percent (%) sleep at night, mean (SD)	87.31 (5.35)
Metabolic Markers	
Hypertension, n (%)	99 (80.50)
Dyslipidemia, n (%)	74 (61.70)
Type 2 Diabetes, n (%)	23 (19.17)

[1]Includes heart attack, heart failure, angina, heart disease, and stroke or transient ischemic attack.
[2]Engages in ≥30 minutes of moderate intensity physical activity on 5 or more days of the week.

Table 2.2. Odds ratios of type 2 diabetes, dyslipidemia, and hypertension by sleep parameters in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		Diabetes	Dyslipidemia	Hypertension
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Number with Condition (%)		23 (19.2)	74 (61.7)	99 (80.5)
Nighttime sleep duration (hours)	Model 1	0.96 (0.61, 1.49)	0.85 (0.59, 1.22)	0.96 (0.62, 1.49)
	Model 2	0.92 (0.57, 1.49)	0.85 (0.59, 1.23)	0.96 (0.61, 1.52)
	Model 3	0.92 (0.56, 1.53)	0.83 (0.57, 1.20)	0.97 (0.62, 1.52)
Daytime sleep duration (hours)	Model 1	1.80 (0.89, 3.64)	0.75 (0.40, 1.39)	1.19 (0.51, 2.81)
	Model 2	1.61 (0.75, 3.49)	0.69 (0.36, 1.32)	1.04 (0.42, 2.57)
	Model 3	1.75 (0.74, 4.11)	0.64 (0.33, 1.24)	1.10 (0.44, 2.74)
Percent sleep at night (%)	Model 1	0.94 (0.86, 1.02)	0.99 (0.92, 1.06)	1.01 (0.93, 1.11)
	Model 2	0.94 (0.85, 1.04)	0.99 (0.92, 1.06)	1.02 (0.93, 1.12)
	Model 3	0.93 (0.83, 1.03)	0.99 (0.92, 1.07)	1.02 (0.93, 1.11)

Model 1 – Adjusted for age and gender.
Model 2 – Adjusted for variables in Model 1 + physical activity, alcohol, smoking, and BMI.
Model 3 – Adjusted for variables in Model 2 + Role Overload and depression (CESD-10) scores.

Table 2.3. Odds ratios of type 2 diabetes, dyslipidemia, and hypertension by combined sleep groups (nighttime sleep duration *with* percent sleep at night) in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		<7 or >8 hours & <85% sleep at night	**<7 or >8 hours & ≥85% sleep at night**	**7-8 hours & <85% sleep at night**	**7-8 hours & ≥85% sleep at night**
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**Reference**
Number (%)		18 (14.3)	55 (43.7)	12 (9.5)	33 (26.2)
Diabetes	Model 1	1.76 (0.36, 8.58)	1.25 (0.38, 4.15)	1.06 (0.17, 6.77)	--
	Model 2	1.47 (0.25, 8.54)	1.11 (0.30, 4.16)	0.70(0.10, 5.05)	--
	Model 3	1.07 (0.17, 6.63)	0.92 (0.23, 3.63)	0.66 (0.09, 5.17)	--
Dyslipidemia	Model 1	1.46 (0.37, 5.78)	0.76 (0.30, 1.90)	0.46 (0.11, 1.86)	--
	Model 2	1.54 (0.37, 6.35)	0.78 (0.30, 2.01)	0.46 (0.11, 1.89)	--
	Model 3	1.31 (0.30, 5.66)	0.70 (0.27, 1.84)	0.46 (0.11, 2.02)	--
Hypertension	Model 1	3.24 (0.56, 18.83)	2.11 (0.66, 6.69)	0.33 (0.07, 1.50)	--
	Model 2	2.91 (0.48, 17.53)	2.02 (0.60, 6.80)	0.22 (0.04, 1.19)	--
	Model 3	3.10 (0.51, 18.94)	2.12 (0.62, 7.21)	0.26 (0.05, 1.37)	--

Model 1 – Adjusted for age and gender.
Model 2 – Adjusted for variables in Model 1 + physical activity, alcohol, smoking, and BMI.
Model 3 – Adjusted for variables in Model 2 + Role Overload and depression (CESD-10) scores.

Table 2.4. Odds ratios of type 2 diabetes, dyslipidemia, and hypertension by combined sleep groups (daytime sleep duration *with* percent sleep at night) in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		≥30 minutes of daytime & <85% sleep at night	**≥30 minutes of daytime & ≥85% sleep at night**	**<30 minutes of daytime & <85% sleep at night**	**<30 minutes of daytime & ≥85% sleep at night**
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**Reference**
Number (%)		15 (12%)	56 (44%)	15 (12%)	32 (25%)
Diabetes	Model 1	2.19 (0.48, 9.94)	1.09 (0.33, 3.58)	0.42 (0.04, 4.27)	--
	Model 2	1.72 (0.32, 9.13)	0.88 (0.24, 3.27)	0.25 (0.02, 3.05)	--
	Model 3	2.56 (0.43, 15.32)	1.35 (0.33, 5.58)	0.22 (0.02, 2.94)	--
Dyslipidemia	Model 1	0.55 (0.14, 2.13)	0.60 (0.23, 1.55)	1.06 (0.26, 4.40)	--
	Model 2	0.48 (0.12, 1.97)	0.55 (0.21, 1.46)	1.26 (0.27, 5.80)	--
	Model 3	0.53 (0.12, 2.31)	0.63 (0.23, 1.74)	1.25 (0.26, 6.02)	--
Hypertension	Model 1	0.71 (0.11, 4.57)	0.58 (0.17, 1.96)	0.41 (0.09, 1.85)	--
	Model 2	0.55 (0.08, 3.80)	0.52 (0.15, 1.81)	0.31 (0.06, 1.53)	--
	Model 3	0.58 (0.08, 4.16)	0.54 (0.14, 2.03)	0.31 (0.06, 1.60)	--

Model 1 – Adjusted for age and gender.
Model 2 – Adjusted for variables in Model 1 + physical activity, alcohol, smoking, and BMI.
Model 3 – Adjusted for variables in Model 2 + Role Overload and depression (CESD-10) scores.

Table 2.5. Odds ratios of type 2 diabetes, dyslipidemia, and hypertension by combined nighttime *and* daytime sleep duration groups in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		<7 or >8 hours at night & ≥30 minutes of daytime sleep	**<7 or >8 hours at night & <30 minutes of daytime sleep**	**7-8 hours at night & ≥30 minutes of daytime sleep**	**7-8 hours at night & <30 minutes of daytime sleep**
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**Reference**
Number (%)		48 (38.1)	25 (19.8)	23 (18.3)	22 (17.5)
Diabetes	Model 1	2.13 (0.41, 11.12)	1.57 (0.24, 10.07)	1.75 (0.28, 10.99)	--
	Model 2	1.85 (0.31, 11.09)	1.27 (0.17, 9.32)	1.31 (0.17, 9.90)	--
	Model 3	2.55 (0.38, 17.33)	1.28 (0.16, 10.47)	2.84 (0.30, 26.50)	--
Dyslipidemia	Model 1	0.60 (0.20, 1.86)	0.91 (0.25, 3.34)	0.46 (0.13, 1.68)	--
	Model 2	0.48 (0.15, 1.60)	0.76 (0.20, 2.95)	0.34 (0.09, 1.38)	--
	Model 3	0.49 (0.14, 1.71)	0.72 (0.18, 2.94)	0.46 (0.11, 1.98)	--
Hypertension	Model 1	2.42 (0.24, 7.92)	1.22 (0.31, 6.22)	2.12 (0.48, 9.32)	--
	Model 2	2.43 (0.70, 8.44)	1.31 (0.27, 6.33)	2.23 (0.45, 11.00)	--
	Model 3	2.40 (0.67, 8.62)	1.31 (0.26, 7.51)	2.40 (0.44, 13.11)	--

Model 1 – Adjusted for age and gender.
Model 2 – Adjusted for variables in Model 1 + physical activity, alcohol, smoking, and BMI.
Model 3 – Adjusted for variables in Model 2 + Role Overload and depression (CESD-10) scores.

Figure Legend

Figure 2.1. Daytime sleep duration does not significantly differ by type 2 diabetes, dyslipidemia, or hypertension status in a sample of elderly Alzheimer's caregivers (N=126), unadjusted.

Figure 2.2. Nighttime sleep duration does not significantly differ by type 2 diabetes, dyslipidemia, or hypertension status in a sample of elderly Alzheimer's caregivers (N=126), unadjusted.

Figure 2.3. Nighttime sleep efficiency does not significantly differ by type 2 diabetes, dyslipidemia, or hypertension status in a sample of elderly Alzheimer's caregivers (N=126), unadjusted.

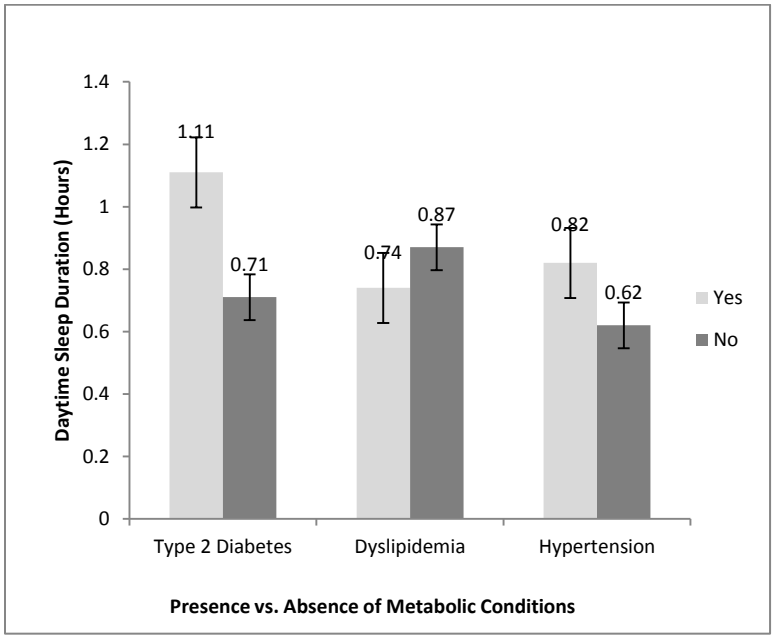

Figure 2.1. Daytime sleep duration does not significantly differ by type 2 diabetes, dyslipidemia, or hypertension status in a sample of elderly Alzheimer's caregivers (N=126), unadjusted.

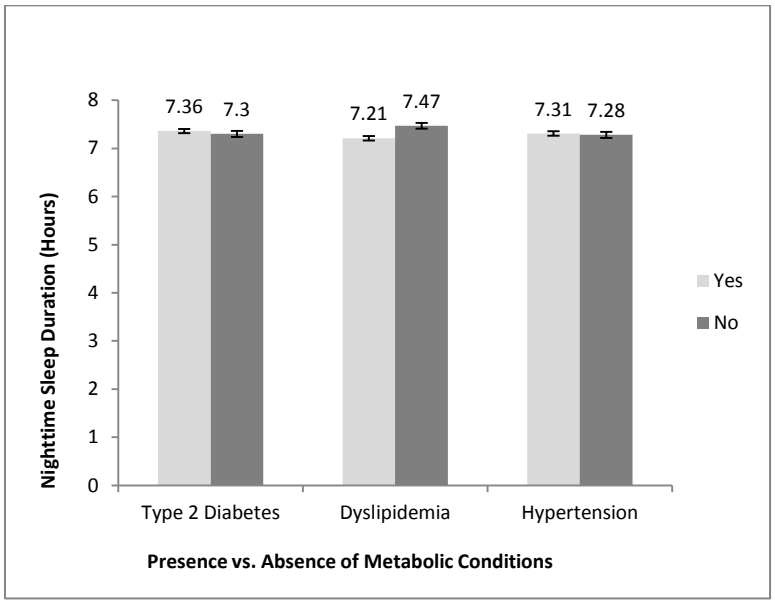

Figure 2.2. Nighttime sleep duration does not significantly differ by type 2 diabetes, dyslipidemia, or hypertension status in a sample of elderly Alzheimer's caregivers (N=126), unadjusted.

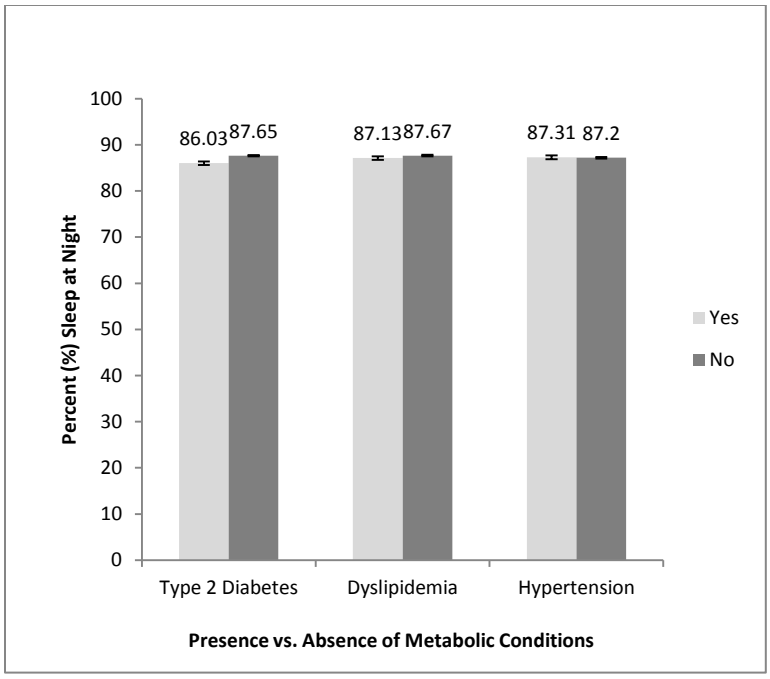

Figure 2.3. Nighttime sleep efficiency does not significantly differ by type 2 diabetes, dyslipidemia, or hypertension status in a sample of elderly Alzheimer's caregivers (N=126), unadjusted.

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CHAPTER 3: Nighttime Sleep Duration and Efficiency Associated with Plasma Catecholamine Concentrations in Elderly Alzheimer's Caregivers

Title: Nighttime Sleep Duration and Efficiency Associated with Plasma Catecholamine Concentrations in Elderly Alzheimer's Caregivers

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Abstract

Background: Research suggests that very short or long durations of sleep and inefficient sleep, are associated with changes in cardiovascular disease (CVD) biomarkers.

Objectives: This study tested the hypothesis that sleep duration and efficiency are associated with plasma catecholamine concentrations in a sample of community-dwelling elderly Alzheimer's caregivers.

Methods: Participants were 126 caregivers for spouses with Alzheimer's disease who underwent in-home sleep assessment by wrist actigraphy for 72 consecutive hours with data averaged across the 3 days/nights. Nighttime sleep and daytime napping were computed. Morning fasting blood samples were collected in participants' homes to determine catecholamine concentrations.

Results: Linear regression models including covariates related to sleep and cardiovascular disease (CVD) indicated that nighttime sleep efficiency (defined as percent sleep at night) was significantly associated with morning plasma dopamine levels (B=0.04, p=0.002). Also, caregivers with <85% sleep at night had significantly lower levels of plasma dopamine (B=-0.49, p=0.003), epinephrine (B=-0.32, p=0.02), and norepinephrine (B=-0.24 p=0.04) compared to caregivers with ≥85% sleep at night in fully adjusted models. When combinations of sleep parameters were examined in fully adjusted models, among caregivers who slept 7-8 hours at night, those with <85% sleep at night had lower dopamine and epinephrine levels (B=-0.80, p=0.002 and B=-0.44, p=0.05, respectively) compared to those with ≥85% sleep at night. Among caregivers who slept <30 minutes during the day, those with <85% sleep at night had lower levels of epinephrine and norepinephrine (B=-0.52, p=0.02 and B=-0.040, p=0.03, respectively) compared to those with ≥85% sleep at night.

Conclusions: These analyses indicate that greater nighttime sleep efficiency and duration are associated with increased morning plasma catecholamine concentrations in

elderly Alzheimer's Caregivers. The increased risk of CVD associated with caregiving could be mediated by the effect of habitually insufficient sleep on catecholamine secretion. Larger longitudinal studies with non-invasive, objective sleep measures examining the effects of sleep on plasma catecholamine concentrations in elderly participants are recommended.

Introduction

Sleep has been shown to be shorter and more disturbed in Alzheimer's caregivers compared to non-caregivers, presumably due to challenges associated with caregiving.[1-3] Caring for a spouse with Alzheimer's disease has also been associated with increased risk for cardiovascular disease (CVD) and death.[4-7] The increased risk of CVD may be due to the effect that insufficient sleep has on numerous physiologic processes that can stress the cardiovascular system.[3, 8-10,11] Indeed, chronically inadequate sleep has been shown to be an independent predictor of CVD risk.[12] Frequent awakenings and disruptions during sleep can lead to a state of prolonged and heightened sympathoadrenal medullary (SAM) arousal.[13-16] For example, caregivers have exhibited raised concentrations of basal plasma catecholamines compared to non-caregivers, which reflect SAM activity.[17] This SAM hyperactivity is thought to promote pathologic processes related to the initiation and progression of vascular and cardiac diseases.[14, 18, 19] Therefore, the increased risk of CVD associated with caregiving could be mediated by the effect of habitually insufficient sleep on catecholamine secretion.[12, 20]

Sleep curtailment and/or inefficient sleep have been associated with altered concentrations of norepinephrine and epinephrine.[13, 14, 21-23] Norepinephrine, a catecholamine released from the adrenal medulla and sympathetic neurons, increases with age and acts as a neurotransmitter and hormone.[24] Epinephrine, another catecholamine that acts as a hormone and neurotransmitter, is released only from the adrenal glands and tends to decrease with age.[24] Actions of these catecholamines vary by the type of body tissue they are acting upon, but both norepinephrine and epinephrine are synthesized from a metabolic precursor – dopamine –a catecholamine released from the

adrenal gland.[24, 25] All three catecholamines aid in cardiovascular system regulation; and in reaction, adaptation, and survival during stressful circumstances.[26,27] Plasma dopamine has numerous functions, including but not limited to: (1) inhibiting platelet aggregation;[28] (2) aiding in insulin release and its action on tissues;[29, 30] (3) dilating the coronary and renal blood vessels;[31] (4) maintaining proper systemic blood pressure and flow;[30, 31] (5) increasing glomerular filtration and sodium excretion in the kidneys;[32] (6) modulating immune responses;[33] and (7) increasing myocardial contractility and coronary artery perfusion, thereby optimizing cardiac performance.[34, 35] Therefore, insufficient amounts of dopamine are hypothesized to increase the risk of CVD.[36, 37]

Several studies have focused on associations of sleep with plasma epinephrine and norepinephrine, yet none have examined associations between sleep and plasma dopamine.[13, 14, 38] For example, data reported by Irwin et al. indicated that experimentally induced partial sleep deprivation (3.75 hours of sleep), measured polysomnographically in 17 men (mean age of 39 years), resulted in increased morning epinephrine and norepinephrine levels compared to a baseline night of 6.7 hours.[13] Conversely, analyses from other sleep restriction studies reported either no significant changes in plasma catecholamine concentrations, or a slight decrease, after a night of sleep deprivation.[39, 40] For example, data from a small study (n=8, mean age of 40 years) indicated that morning levels of plasma epinephrine and norepinephrine did not change after a night of total sleep deprivation compared to a normal night of 7.1 hours of sleep.[40] A partial-night sleep deprivation study on 36 abstinent alcohol-dependent men and 36 matched controls revealed that the control participants (mean age of 44 years) had lower morning levels of

circulating epinephrine after a night of partial sleep deprivation (3.5 hours of sleep) than after the baseline and recovery sleep nights (7.5 hours of sleep).[41]

Studies to date have reported inconsistent relationships between sleep and catecholamine concentrations from widely varying research methods and participant characteristics.[26, 42] Most reports were based on experimentally induced sleep deprivation – procedures that could be independent stressors and not indicative of long-term patterns.[26] Therefore, the increased SAM activity reported in some of these studies could be due to the stressful sleep deprivation methods themselves, or it could be a consequence of sleep loss.[26] The objective of this cross-sectional analysis was to examine whether habitual sleep duration and efficiency were associated with morning plasma catecholamine concentrations, evaluated objectively in the home, among 126 community-dwelling elderly spousal Alzheimer's caregivers who participated in the Alzheimer Caregiver Coping Study.

Methods

The Alzheimer Caregiver Coping Study

The Alzheimer Caregiver Coping Study was conducted at the University of California, San Diego (UCSD) to examine relationships between physiological and psychological stress markers, and health risk factors in spousal Alzheimer's caregivers. All data were collected between 2007 and 2010.

Participants were 126 community-dwelling men and women over the age of 55 years who were living with, and providing continuous in-home care to a spouse diagnosed with Alzheimer's disease. Participants were recruited via referrals from the UCSD Alzheimer's Disease Research Center, community Alzheimer caregiver support

groups, local agencies serving caregivers, recommendations from other participants enrolled in the study, flyers, media advertisements, and senior health fairs. Participants provided written informed consent, and the study was approved by the UCSD Institutional Review Board.

Caregivers were excluded if they had a current diagnosis or treatment for a life-threatening or terminal medical condition that required ongoing care (i.e. advanced CVD, Parkinson's disease, and/or a severe psychiatric disorder), extreme hypertension (>200/120 mm Hg), current or recent (within the past 5 years) treatment for cancer, organ transplantation requiring anti-rejection medication, or use of corticosteroids, β-blocking, and/or anticoagulant medication.

Measures

All measurements and assessments, other than objective measures of sleep, were administered between 9:00AM and 11:00AM in participants' homes by trained research personnel.

Sociodemographics, Medical Data, and Past Health History

The research assistant administered a semi-structured interview that gathered information on sociodemographics, medical history, health behaviors (e.g. smoking status and physical activity), and hospitalizations. Caregivers were asked if they had ever been told by a physician that they had type 2 diabetes, hypertension, dyslipidemia, myocardial infarction, heart failure, chest pain (angina), heart disease, transient ischemic attack and/or stroke, with answers coded yes/no. Information about cardiovascular medication (i.e., aspirin, angiotensin-converting enzyme inhibitors, and statins) and antidepressant use (i.e., atypicals, selective serotonin reuptake inhibitors, tricyclics, etc.) was obtained

via self-report and confirmed by examination of the medication containers. Height and weight were obtained by participant report, and body mass index (BMI) was calculated as the ratio of weight in kilograms to height in meters squared. Blood pressure was measured three times using a non-invasive Microlife BP monitor (model number 3AC1-1PC) with the caregiver in a supine position. The average of the three measurements was used to create a composite resting blood pressure estimate.

History of cardiovascular disease (coded yes/no) was defined as previous heart attack, heart failure, angina, heart disease, stroke, or transient ischemic attack. Smoking status was categorized as current/former smoker vs. never smoker and also measured in terms of years of smoking. Alcohol consumption was quantified in terms of the number of alcoholic drinks consumed per week. Participants with a BMI > 30 were classified as obese. Hypertension (coded yes/no) was defined either by self-report of physician-diagnosed hypertension and current use of a prescription antihypertensive, or as a resting diastolic blood pressure or systolic blood pressure ≥90 or ≥140 mmHg, respectively. Dyslipidemia (coded yes/no) was defined either by total-to-HDL ratio >5, or by self-report of current use of prescription cholesterol-lowering medications. Type 2 diabetes (coded yes/no) was defined either by caregiver report of physician-diagnosed diabetes and current use of antiglycemic medication, or a fasting blood glucose ≥126 mg/dL, as classified by the American Diabetes Association.[43]

Psychological Questionnaires

The semi-structured interview included questionnaires that evaluated duration of caregiving, psychological distress, perceived stress, depressive symptom severity, and anxiety and depressive symptoms. Duration of caregiving was determined by the self-

reported amount of time in years that had elapsed since the spouse was diagnosed with Alzheimer's disease. The 10-item short form of the Center for Epidemiologic Studies Depression Scale (CESD-10) was used to assess depressive symptoms.[44-46] Levels of life stress were assessed with the 4-item Role Overload Scale, a self-report 4-point Likert scale ranging from 1=not at all to 4=completely, which measured the extent to which participants felt overwhelmed by everyday tasks. Lower role overload and CESD-10 scores indicate lower stress and depressive symptoms, respectively. Reliability (Cronbach's alpha) for the 4-item Role Overload Scale has ranged from 0.71 to 0.77 in different samples of elderly caregivers,[47] however in our sample, the alpha coefficient is 0.82. Cronbach's alpha for the CESD-10 in our sample of caregivers is 0.52.

Objective Sleep Measure

Objective sleep/wake activity was measured with the Actiwatch-Light® (Mini Mitter Co., Inc, a Respironics, Inc. Co., Bend, OR), which was worn for 72 consecutive hours (three consecutive 24-hour periods) on participants' non-dominant wrist. Actigraphy has been validated in and recommended for use among elderly populations and has been compared favorably with polysomnography, which is deemed the gold standard for sleep assessment.[48, 49] The Actiwatch-Light® uses a piezoelectric linear accelerometer (sensitivity <.01 g-force) with a sampling rate of 32Hz to measure and record wrist movement. Movement, which was measured as the number of accelerations per minute, was captured via internal motion sensors in the watch. Calculating wrist activity over time allowed for an objective measure of duration and disruption of sleep. The recorded actigraphy data were analyzed using Actiware® sleep and activity monitoring software (version 5, by Mini Mitter|Respironics/Philips). Sleep diaries

completed by participants estimated times the actigraphy watch was removed, bedtimes, and wake times, and were used for editing the actigraphy data.

The following sleep parameters were averaged across the three consecutive 24-hour time periods and selected a priori: 1) total nighttime sleep duration (hours per night spent sleeping from reported bedtime to final uptime); 2) total hours of daytime sleep (nap time), with naps defined as no activity for a minimum of 10 minutes; and 3) percent of time asleep at night between initial sleep onset and final awakening, which was used to denote sleep efficiency.

Outcomes - Catecholamine Collection Procedures

Fasting venous blood was drawn within one week of the initial visit between 9:00AM and 11:00AM to decrease the impact of diurnal fluctuations, and the first blood draw took place after 10 minutes of rest in the supine position. Blood was drawn with a 22-gauge indwelling venous catheter inserted into the participant's forearm, and collected in syringes that contained EDTA or sodium citrate; the first 2 ml of blood were discarded. All blood samples were centrifuged twice at room temperature for 15 minutes, and then immediately stored in plastic tubes containing 1 ml aliquots at -80°C until analyzed.

A catechol-O-methyltransferase (COMT) radioenzymatic assay was used to extract dopamine, epinephrine, and norepinephrine from 0.5 ml of plasma and concentrate them into 0.1 ml of dilute acid. This technique has an 81% efficiency rate, removes Ca 2+ and other components that inhibit the COMT assay, and has been shown to be 10 times more sensitive than routinely conducted basic catecholamine assays.[50]

Statistical Analysis

To better approximate a normal distribution, all catecholamine values were logarithmically transformed. Associations between continuous sleep measures, plasma catecholamines, and key covariates (e.g. physical activity) were tested using Pearson *r* and t-tests, which identified potential confounders. Multivariate linear regression was used to identify the sleep parameters that were significantly associated with the catecholamines (dopamine, epinephrine and norepinephrine, separately) independent of covariates. In the regression models, covariates were restricted to age, gender, variables showing significant ($p<0.10$) univariate correlations with the exposure variables (sleep parameters) or the outcome variables (catecholamines), and variables selected a-priori as likely related to CVD and sleep.

Three separate models were created to examine changes in the sleep-catecholamine relationships as related groups of covariates were added. Covariates adjusted for in the first model (Model 1) included age and gender. In the second multivariate model (Model 2) BMI, physical activity, alcohol consumption, hypertension, diabetes, dyslipidemia, and history of CVD were added to the model. In the third model (Model 3), Role overload score, depression (CESD-10) score, and duration of caregiving were added in addition to the covariates specified in Model 2. First, the sleep variables were treated as continuous. In secondary analyses, to test for non-linear associations or thresholds, sleep parameters were modeled categorically and by combining sleep parameters into three new variables: 1) nighttime sleep duration *with* daytime sleep duration; 2) nighttime sleep duration *with* percent sleep at night; and 3) daytime sleep duration *with* percent sleep at night. In these secondary analyses, reference groups were chosen based on current clinically significant cut points of these sleep parameters in

elderly adults, and daytime sleep duration was reported in minutes for ease of interpretation. Specifically, 7-8 hours of sleep at night, ≥85% sleep at night, and <30 minutes of daytime sleep are generally considered the normal cut-offs for elderly adults, and were therefore used as the reference groups and/or cut points.[48, 51, 52]

To account for Type I error inflation due to the large number of sleep parameters and catecholamines under consideration, we applied a Bonferroni correction for 9 hypothesis tests (3 sleep variables and 3 catecholamines). A p-value less than 0.05/9=0.0056 would be considered significant after such a correction. However, this adjustment is likely overly stringent since many of the variables (e.g. the 3 catecholamines) are likely to be correlated with each other. Hence, we present the inferential results for all the models, and mark those that are below the Bonferroni threshold p-value in the footnotes to the tables. This study specified a significance level of 0.05 or below (2-tailed) in the multivariate models, and all statistical analyses were conducted using SPSS version 19.0 statistical package.

Results

Participant Characteristics

Demographic and health characteristics for the sample of Alzheimer's caregivers are presented in Table 3.1. Caregivers were a mean age of 74 years, primarily women (71%), Caucasian (92%), slightly overweight, and had been providing care for an average of 4.3 years. The majority of caregivers had hypertension (81%) and dyslipidemia (62%), while 19% were found to have Type 2 diabetes, and 20% had a history of cardiovascular disease. On average, caregivers slept 7 hours and 20 minutes and were asleep for 87% of the night, and spent 48 minutes napping.

Continuous Sleep Parameters and Catecholamines

In unadjusted analyses (table not shown), nighttime sleep duration and percent sleep at night were positively associated with plasma dopamine ($p<0.05$ for both); there were no significant associations between any of the sleep parameters and epinephrine or norepinephrine. Table 3.2 shows that after adjusting for age and gender (Model 1), nighttime sleep duration was significantly associated with plasma dopamine levels. Specifically, a 1 hour increase in nighttime sleep duration was associated with 1.12 pg/mL higher dopamine levels ($p=0.05$; the regression coefficient $B=0.11$ pg/mL in the model with log-transformed outcomes). However, with additional adjustment for covariates in models 2 and 3, this relationship was attenuated and no longer statistically significant ($p=0.08$ and $p=0.11$, respectively). Nighttime sleep duration measured continuously was not significantly associated with epinephrine or norepinephrine.

As shown in Table 3.2, in all three models, percent sleep at night was significantly associated with plasma dopamine levels ($p<0.005$ for all) such that if percent sleep at night was increased by 1%, dopamine levels increased by 1.04 pg/mL ($B=0.04$ pg/mL when log transformed). Model 3 explained about 23% of the variance in plasma dopamine levels ($R^2=0.229$). Percent sleep at night measured continuously was not significantly associated with epinephrine or norepinephrine, and daytime sleep duration was not significantly associated with concentrations of any of the catecholamines.

Categorical Sleep Parameters and Catecholamines

As shown in Figure 3.1, in all three adjusted models, caregivers with <85% sleep at night had significantly lower levels of plasma dopamine (Model 1: $B=-0.44$, $p=0.005$;

Model 2: B=-0.48, p=0.003; and Model 3: B=-0.49, p=0.003), epinephrine (Model 1: B=-0.34, p=0.01; Model 2: B=-0.33, p=0.02; and Model 3: B=-0.32, p=0.02) and norepinephrine (Model 1: B=-0.25, p=0.03; Model 2: B=-0.25, p=0.03; and Model 3: B=-0.24, p=0.04) compared to caregivers with ≥85% sleep at night. Catecholamine concentrations did not significantly differ by nighttime (<7 or >8 hours *vs.* 7-8 hours) or daytime (<30 minutes *vs.* ≥30 minutes) sleep duration groups (figures not shown).

Associations between combined sleep parameters and the three catecholamines are shown in Tables 3.3-3.5. As shown in Table 3.3, in all three adjusted models, caregivers with 7-8 hours of nighttime sleep *and* <85% sleep at night had significantly lower levels of plasma dopamine compared to caregivers with 7-8 hours of nighttime sleep *and* ≥85% sleep at night ($p<0.01$ for all). Also, in all three models, caregivers with 7-8 hours of nighttime sleep *and* <85% sleep at night had significantly lower levels of plasma epinephrine compared to caregivers with 7-8 hours of nighttime sleep *and* ≥85% sleep at night ($p<0.05$ for all).

As shown in Table 3.4, when adjusting for covariates in all 3 models, caregivers with <30 minutes of daytime sleep *and* <85% sleep at night had significantly lower levels of epinephrine and norepinephrine compared to caregivers with <30 minutes of daytime sleep *and* ≥85% sleep at night ($p<0.05$ for all). Catecholamine concentrations did not significantly differ by combined nighttime and daytime sleep duration groups (Table 3.5).

Discussion

In this sample of community-dwelling elderly Alzheimer's caregivers, the primary results indicate that greater nighttime sleep efficiency (defined as percent sleep at night) was significantly associated with increased morning concentrations of plasma

dopamine after adjustment for covariates related to sleep and CVD. Also, nighttime sleep duration was significantly associated with increased morning plasma dopamine levels after adjustment for age and gender. To our knowledge, no studies have investigated relationships between sleep and plasma dopamine concentrations. Since insufficient amounts of plasma dopamine may contribute to increased risk of developing CVD,[30, 36, 37] these results add to data indicating that insufficient sleep at night is associated with increased risk of CVD.[53-56] Perhaps older caregivers with efficient sleep have heightened plasma dopamine levels, and in turn are at lower risk of CVD and better equipped to react to and manage everyday challenges via increased catecholamine responses. For example, when plasma dopamine is released, coronary and renal blood vessels dilate and coronary artery perfusion increases.[31, 34, 35]

Secondary analyses with categorical sleep parameters indicate that caregivers with <85% sleep at night had significantly lower levels of plasma dopamine, epinephrine and norepinephrine compared to caregivers with ≥85% sleep at night. Similarly, analyses with combined sleep parameters indicated that among caregivers who slept 7-8 hours at night, those with a sleep efficiency <85% at night had significantly lower levels of morning plasma dopamine and epinephrine compared to those with a sleep efficiency ≥85% at night; and among those who slept <30 minutes during the day, those with a sleep efficiency <85% at night had significantly lower levels of plasma epinephrine and norepinephrine compared to those with a sleep efficiency ≥85% at night. These findings were unexpected with regards to plasma epinephrine and norepinephrine, as they contradict published studies suggesting a positive association of sleep disturbance or fragmentation with plasma epinephrine and norepinephrine.[14, 57] For example, a cross-

sectional study from our laboratory on Alzheimer's caregivers (n=40, mean age of 73 years) indicated that longer polysomnographically measured wake time after sleep onset (WASO), which indicates sleep disturbance and was highly correlated with percent sleep at night in our study (r=-0.93), was associated with elevated concentrations of plasma norepinephrine.[14]

Nevertheless, we cannot easily compare our results with published data, as previous trials have either measured sleep for one night with polysomnography, included younger participants and/or only men, measured catecholamine levels at night, or collected catecholamines from urine.[14, 57-59] For example, data by Zhang et al. indicated that actigraphically measured inefficient sleepers (defined as <85% sleep at night) with a mean age of 41 years had higher 24-hour urinary epinephrine and norepinephrine.[59] Although this study used actigraphy to evaluate sleep efficiency, 24-hour urine samples were used to measure catecholamines rather than morning blood samples, and the participants were about 34 years younger than the caregivers in our sample.[59] Urine and plasma catecholamine concentrations cannot be straightforwardly compared, as the smaller urine catecholamine concentrations are determined by the amount excreted over a 24-hour period, while the larger plasma catecholamine concentrations are determined by the amount present in the blood at the moment of collection.[32] Similarly, data on 62 men with a mean age of 45 years indicated that polysomnographically measured sleep efficiency (defined as percent sleep at night) was negatively correlated with nocturnal (10PM–6AM) plasma norepinephrine levels.[58] Again, it is difficult to compare these data with our own, as they included younger men, one night of polysomnography to measure

sleep, and nocturnal catecholamines that were evaluated every 30 minutes throughout the night.[58]

Our findings that caregivers with efficient sleep had higher morning plasma epinephrine and norepinephrine concentrations are difficult to explain, but heightened catecholamine activity may be beneficial for cardiovascular health in elderly individuals. For example, higher catecholamine concentrations in the elderly may reflect a compensatory mechanism for a declining peripheral pressor sensitivity to SAM stimuli rather than a primary hyper-sympathoadrenal medullary state.[60, 61] Alternatively, chronically poor sleep may suppress SAM activity – a theory that has been demonstrated in animal studies.[26, 62] On the other hand, increased morning plasma catecholamine levels may be an indication of larger fluctuations in epinephrine and norepinephrine during a 24 hour period, with greater sympathetic responsiveness in elderly caregivers with efficient sleep.[60] However, to verify this, catecholamine levels would have needed to be sampled throughout a 24-hour period. Lastly, blunted nighttime blood pressure dipping, which predicts harmful CVD outcomes and is correlated with poor sleep efficiency, has been associated with reduced morning plasma norepinephrine levels.[63-65] Therefore, increased morning plasma catecholamine levels could be partially explained by heightened nocturnal blood pressure dipping in caregivers with efficient sleep. However, we would have needed to monitor blood pressure throughout the night to confirm this.

To our knowledge, these are the first analyses to investigate relationships between sleep and plasma dopamine, and to examine associations of combined sleep parameters with catecholamine concentrations. This study, which obtained non-invasive, objective measurements of sleep for an extended period of time via actigraphy in a naturalistic,

real-life setting, adds to the small yet conflicting body of literature that focuses on sleep and catecholamine concentrations in older adults. Meanwhile, the majority of published data that indicated significant correlations between insufficient sleep and catecholamines are based on short-term sleep deprivation simulated in a laboratory, which may not be representative of habitual sleep, and is not the same as chronic partial sleep deprivation experienced in real-life.[66] Given the inconsistency of the current literature, additional studies with non-invasive and objectively measured sleep are warranted to help clarify relationships between sleep and plasma catecholamine concentrations in elderly adults.

Limitations

This sample of caregivers had relatively undisturbed sleep, they were not considered sleep deprived, and there was limited variance in the sleep variables.[51, 67] Associations between sleep and catecholamines may have differed if our sample of caregivers had pathological sleep disturbances and/or a greater variance in sleep patterns. Due to the cross-sectional design of the study, inferences regarding causality or directionality of relationships between the sleep parameters and catecholamine concentrations cannot be determined.

Conclusions

The current analyses suggest that habitual nighttime sleep duration and efficiency (defined as percent sleep at night) were positively associated with morning plasma catecholamine concentrations in a sample of community-dwelling elderly Alzheimer's caregivers, thereby implicating a role for sleep in SAM regulation. Chronically insufficient sleep may alter SAM activity, and more specifically plasma catecholamines, which in turn may mediate the relationship between insufficient sleep and adverse

cardiovascular health in elderly caregivers. Experimental studies with larger samples and objective sleep measures that aim to extend nighttime sleep duration and improve sleep efficiency are needed to examine whether concentrations of plasma catecholamines are altered in elderly adults, and in turn, whether downstream harmful CVD outcomes are reduced.

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Table 3.1. Characteristics of a sample of elderly Alzheimer's caregivers (N=126) in a study of the associations of sleep with plasma catecholamine concentrations

Age (years), mean (SD)	74.16 (7.98)
Female, n (%)	89 (71.20)
Ethnicity, n (%)	
Caucasian	115 (92.00)
Non-Caucasian	10 (8.00)
Education (years), mean (SD)	15.15 (3.05)
Body mass index (kg/m^2), mean (SD)	26.49 (4.71)
Systolic blood pressure (mmHg), mean (SD)	134.3 (15.3)
Diastolic blood pressure (mmHg), mean (SD)	75.8 (8.6)
Blood glucose (mg/dL), mean (SD)	105.1 (43.7)
History of cardiovascular disease, n (%)[1]	25 (19.84)
Duration of caregiving (years), mean (SD)	4.33 (3.38)
Hypertension, n (%)	99 (80.50)
Dyslipidemia, n (%)	74 (61.70)
Type 2 diabetes, n (%)	23 (19.17)
Health Behaviors	
Ever smoker, n (%)	58 (46.03)
Alcohol consumption (drinks/week), mean (SD)	1.40 (1.46)
Meets CDC physical activity recommendation, n (%)[2]	42 (33.30)
Psychological Variables	
Role overload score, mean (SD)	5.18 (3.15)
CESD-10 score, mean (SD)	8.78 (5.81)
Medications	
Current use of antidepressants, n (%)	32 (25.40)
Current use of cholesterol-lowering medication, n (%)	57 (45.20)
Current use of high blood pressure medication, n (%)	76 (60.30)
Current use of diabetes medication, n (%)	15 (11.90)
Objective Sleep Variables	
Nighttime sleep duration (hours), mean (SD)	7.32 (1.12)
Daytime sleep duration (hours), mean (SD)	0.79 (0.67)
Percent (%) sleep at night, mean (SD)	87.31 (5.35)
Blood Plasma Catecholamines[3]	
Dopamine (pg/mL), mean (SD)	52.20 (38.61)
Epinephrine (pg/mL), mean (SD)	39.18 (41.65)
Norepinephrine (pg/mL), mean (SD)	495.22 (237.42)

[1]Includes heart attack, heart failure, angina, heart disease, and stroke or transient ischemic attack.
[2]Partakes in ≥30 minutes of moderate intensity physical activity on 5 or more days of the week.
[3]Biomarker values are displayed as original, untransformed data.

Table 3.2. Relationships between continuously measured sleep parameters and log transformed plasma catecholamine concentrations in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		Dopamine		**Epinephrine**		**Norepinephrine**	
		B (95% CI)	***p***	**B (95% CI)**	***p***	**B (95% CI)**	***p***
Nighttime sleep duration (hours)	1	0.11 (0.00, 0.23)	0.05*	0.07 (-0.04, 0.17)	0.20	0.05 (-0.04, 0.13)	0.29
	2	0.10 (-0.01, 0.22)	0.08	0.07 (-0.03, 0.17)	0.19	0.05 (-0.04, 0.13)	0.30
	3	0.10 (-0.02, 0.21)	0.11	0.06 (-0.05, 0.16)	0.29	0.03 (-0.05, 0.12)	0.43
Daytime sleep duration (hours)	1	0.13 (-0.08, 0.33)	0.23	-0.01 (-0.20, 0.17)	0.88	0.04 (-0.11, 0.19)	0.62
	2	0.16 (-0.06, 0.37)	0.15	0.01 (-0.18, 0.20)	0.89	0.05 (-0.11, 0.21)	0.52
	3	0.14 (-0.09, 0.36)	0.22	0.004 (-0.19, 0.19)	0.97	0.05 (-0.12, 0.21)	0.58
Percent (%) sleep at night	1	0.04 (0.01, 0.06)	0.002**	0.02 (-0.003, 0.04)	0.09	0.02 (0.00, 0.03)	0.06
	2	0.04 (0.01, 0.06)	0.004**	0.02 (-0.01, 0.04)	0.13	0.02 (-0.002, 0.03)	0.08
	3	0.04 (0.01, 0.06)	0.002**	0.02 (-0.01, 0.04)	0.12	0.02 (-0.001, 0.03)	0.07

1, Model 1 – Adjusted for age and gender.
2, Model 2 – Adjusted for variables in Model 1 + BMI, physical activity, alcohol consumption, hypertension, dyslipidemia, diabetes, and history of CVD.
3, Model 3 – Adjusted for variables in Model 2 + Role Overload, depression (CESD-10), and duration of caregiving.
*p≤0.05; **Significant after Bonferroni adjustment (p<0.006).

Table 3.3. Associations of combined sleep groups (nighttime sleep duration *with* percent sleep at night) with log transformed catecholamine concentrations in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		<7 or >8 hours & <85% sleep at night	**<7 or >8 hours & ≥85% sleep at night**	**7-8 hours & <85% sleep at night**	**7-8 hours & ≥85% sleep at night**
		B (95% CI)	**B (95% CI)**	**B (95% CI)**	**Reference**
Number (%)		18 (14.3)	55 (43.7)	12 (9.5)	33 (26.2)
Dopamine	1	-0.36 (-0.79, 0.06)	-0.08 (-0.39, 0.22)	-0.69 (-1.17, -0.21)**	--
	2	-0.34 (-0.77, 0.10)	-0.02 (-0.33, 0.29)	-0.73 (-1.22, -0.23)**	--
	3	-0.36 (-0.80, 0.09)	-0.06 (-0.38, 0.26)	-0.80 (-1.30, -0.29)**	--
Epinephrine	1	-0.32 (-0.70, 0.06)	-0.06 (-0.33, 0.21)	-0.46 (-0.89, -0.03)*	--
	2	-0.33 (-0.72, 0.06)	-0.04 (-0.31, 0.24)	-0.44 (-0.87, -0.00)*	--
	3	-0.27 (-0.67, 0.12)	-0.04 (-0.32, 0.25)	-0.44 (-0.88, 0.00)*	--
Norepinephrine	1	-0.26 (-0.56, 0.04)	-0.05 (-0.26, 0.17)	-0.30 (-0.64, 0.04)	--
	2	-0.29 (-0.60, 0.03)	-0.06 (-0.29, 0.17)	-0.29 (-0.66, 0.07)	--
	3	-0.23 (-0.56, 0.09)	-0.05 (-0.28, 0.18)	-0.33 (-0.70, 0.03)	--

1, Model 1 – Adjusted for age and gender.
2, Model 2 – Adjusted for variables in Model 1 + BMI, physical activity, alcohol consumption, hypertension, dyslipidemia, diabetes, and history of CVD.
3, Model 3 – Adjusted for variables in Model 2 + Role Overload, depression (CESD-10), and duration of caregiving.
*p<0.05; **Significant after Bonferroni adjustment (p<0.006).

Table 3.4. Associations of combined sleep groups (daytime sleep duration *with* percent sleep at night) with log transformed catecholamine concentrations in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		≥30 minutes of daytime & <85% sleep at night	≥30 minutes of daytime & ≥85% sleep at night	<30 minutes of daytime & <85% sleep at night	<30 minutes of daytime & ≥85% sleep at night
		B (95% CI)	**B (95% CI)**	**B (95% CI)**	**Reference**
Number (%)		15 (12%)	56 (44%)	15 (12%)	32 (25%)
Dopamine	1	-0.31 (-0.75, 0.12)	0.17 (-0.14, 0.48)	-0.36 (-0.82, 0.10)	--
	2	-0.30 (-0.74, 0.14)	0.19 (-0.13, 0.50)	-0.44 (-0.91, 0.03)	--
	3	-0.30 (-0.75, 0.16)	0.20 (-0.13, 0.53)	-0.47 (-0.95, 0.02)	--
Epinephrine	1	-0.24 (-0.62, 0.15)	-0.09 (-0.36, 0.19)	-0.59 (-1.0, -0.18)**	--
	2	-0.18 (-0.57, 0.21)	-0.03 (-0.30, 0.25)	-0.56 (-0.97, -0.14)[t]	--
	3	-0.18 (-0.57, 0.22)	-0.01 (-0.30, 0.27)	-0.52 (-0.94, -0.11)*	--
Norepinephrine	1	-0.15 (-0.46, 0.15)	-0.07 (-0.28, 0.15)	-0.45 (-0.78, -0.13)[t]	--
	2	-0.16 (-0.48, 0.17)	-0.04 (-0.27, 0.19)	-0.43 (-0.77, -0.09)*	--
	3	-0.15 (-0.48, 0.17)	-0.03 (-0.27, 0.20)	-0.40 (-0.74, -0.05)*	--

1, Model 1 – Adjusted for age and gender.
2, Model 2 – Adjusted for variables in Model 1 + BMI, physical activity, alcohol consumption, hypertension, dyslipidemia, diabetes, and history of CVD.
3, Model 3 – Adjusted for variables in Model 2 + Role Overload, depression (CESD-10), and duration of caregiving.
[t]p<0.01; *p<0.05; **Significant after Bonferroni adjustment (p<0.006).

Table 3.5. Associations of combined nighttime *and* daytime sleep duration groups with log transformed catecholamine concentrations in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates

		<7 or >8 hours at night & ≥30 minutes of daytime sleep	<7 or >8 hours at night & <30 minutes of daytime sleep	7-8 hours at night & ≥30 minutes of daytime sleep	7-8 hours at night & <30 minutes of daytime sleep
		B (95% CI)	**B (95% CI)**	**B (95% CI)**	**Reference**
Number (%)		48 (38.1)	25 (19.8)	23 (18.3)	22 (17.5)
Dopamine	1	0.15 (-0.24, 0.54)	-0.06 (-0.50, 0.38)	0.09 (-0.37, 0.55)	--
	2	0.19 (-0.21, 0.60)	-0.09 (-0.55, 0.37)	0.02 (-0.45, 0.50)	--
	3	0.21 (-0.21, 0.63)	-0.07 (-0.55, 0.40)	0.07 (-0.43, 0.56)	--
Epinephrine	1	0.03 (-0.32, 0.37)	-0.03 (-0.42, 0.36)	0.02 (-0.39, 0.42)	--
	2	0.03 (-0.33, 0.38)	-0.13 (-0.53, 0.28)	-0.03 (-0.45, 0.38)	--
	3	0.07 (-0.29, 0.43)	-0.06 (-0.47, 0.35)	-0.001 (-0.42, 0.42)	--
Norepinephrine	1	-0.02 (-0.29, 0.25)	-0.14 (-0.44, 0.17)	-0.08 (-0.40, 0.24)	--
	2	-0.05 (-0.34, 0.24)	-0.21 (-0.54, 0.12)	-0.12 (-0.46, 0.22)	--
	3	-0.02 (-0.31, 0.28)	-0.15 (-0.48, 0.18)	-0.10 (-0.45, 0.24)	--

1, Model 1 – Adjusted for age and gender.
2, Model 2 – Adjusted for variables in Model 1 + BMI, physical activity, alcohol consumption, hypertension, dyslipidemia, diabetes, and history of CVD.
3, Model 3 – Adjusted for variables in Model 2 + Role Overload, depression (CESD-10), and duration of caregiving.

Figure Legend

Figure 3.1. Elderly Alzheimer's caregivers (N=126) with efficient (≥85%) nighttime sleep have higher plasma catecholamine concentrations compared to caregivers with less efficient (<85%) sleep, adjusted for covariates.

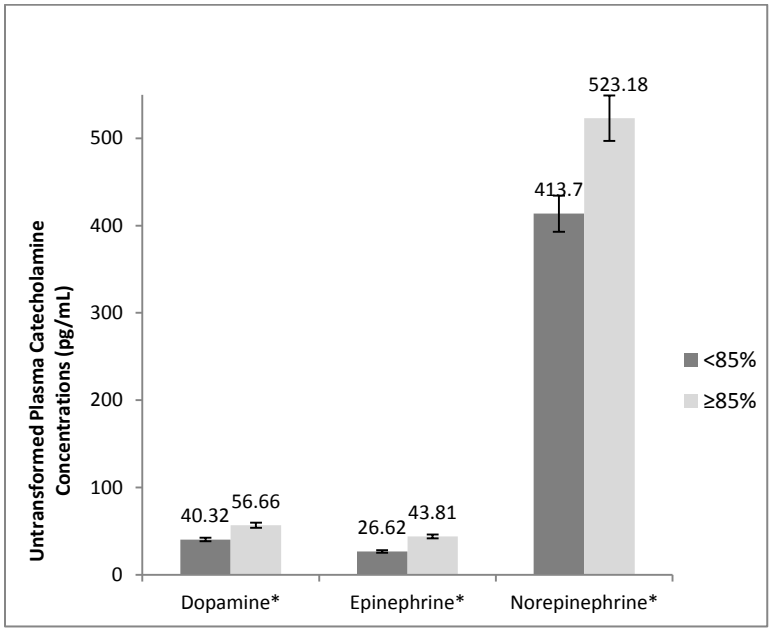

Figure 3.1. Elderly Alzheimer's caregivers (N=126) with efficient (≥85%) nighttime sleep have higher plasma catecholamine concentrations compared to caregivers with less efficient (<85%) sleep, adjusted for covariates.

*In Model 3, dopamine (p=0.003**), epinephrine (p=0.02), and norepinephrine (p=0.04) concentrations significantly differed by nighttime sleep efficiency (percent sleep) group.
**Significant after Bonferroni adjustment (p<0.006).

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CHAPTER 4: Napping and Less Disturbed Nighttime Sleep Associated with Reduced Carotid Intima-Media Thickness in Elderly Alzheimer's Caregivers

Title: Napping and Less Disturbed Nighttime Sleep Associated with Reduced Carotid Intima-Media Thickness in Elderly Alzheimer's Caregivers

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Abstract

Background: Research indicates that very short or long durations of sleep and disturbed sleep, are associated with an increased risk of cardiovascular disease (CVD).

Objectives: This study tested the hypothesis that disturbed or short/long sleep durations are associated with subclinical atherosclerosis, as measured by carotid intima-

media thickness (CIMT), in a sample of community-dwelling elderly Alzheimer's caregivers.

Methods: Participants were 126 caregivers for spouses with Alzheimer's disease who underwent in-home sleep assessment by wrist actigraphy for 72 consecutive hours. Sleep data were averaged across the 3 days/nights; nighttime sleep and daytime napping were computed. Carotid artery ultrasound, also conducted in participants' homes, was used to measure CIMT in millimeters.

Results: Linear regression models including covariates related to sleep and CVD indicated that a longer daytime sleep duration was associated with significantly reduced mean common CIMT (B=-0.04, p=0.02). Specifically, for every additional hour of sleep obtained during the day, mean common CIMT was reduced by 0.04mm. Conversely, greater nighttime wake after sleep onset (WASO) was associated with significantly increased mean common CIMT (B=0.04, p=0.05); for each additional hour of WASO, mean common CIMT increased by 0.04mm. When combinations of sleep parameters were examined, caregivers who slept <30 minutes during the day *and* had ≥1 hour of WASO had significantly greater (B=0.06, p=0.04) mean common CIMT than caregivers who slept <30 minutes during the day *and* had <1 hour of WASO.

Conclusions: These analyses suggest that shorter naps and more disturbed nighttime sleep are associated with increased CIMT. Interventions that enhance sleep quantity and reduce disturbed sleep may decrease the prevalence and extent of subclinical atherosclerosis in older caregivers. Longitudinal studies with objective sleep measures that examine the effects of napping and disturbed sleep on subclinical atherosclerosis are needed.

Introduction

Spouses of Alzheimer's patients may experience frequent awakenings during sleep presumably due to challenges associated with caregiving.[1] This can lead to a state of prolonged and heightened sympathetic arousal,[2] which in turn is thought to promote pathologic processes related to the initiation and progression of atherosclerotic cardiovascular disease.[3-5] Indeed, caregivers have been found to experience more disrupted sleep, and are at increased risk for cardiovascular disease (CVD) and death compared to non-caregivers.[1, 6, 7] The increased risk of CVD could, in part, be due to the effect that inadequate sleep has on numerous physiologic processes that can hasten atherosclerotic progression and risk of CVD.[8, 9,10]

Although the underlying mechanisms of the adverse effects of insufficient sleep on atherosclerosis are not completely understood, numerous pathways have been proposed. Researchers hypothesize that insufficient sleep may cause sympathoadrenal medullary arousal, and elevated inflammatory and coagulation markers, leading to increased coronary artery calcification as well as increased risk for CVD events.[4, 11-14] For example, Werle et al. found that self-reported total hours of sleep (including both nighttime sleep and naps) were inversely related to the 9-year risk of cardiovascular death among a cohort of 187 participants over the age of 80 years.[15] A systematic review of 15 prospective studies by Cappuccio et al. concluded that short (≤5-6 hours) and long (>8-9 hours) sleep durations were significantly associated with increased risk of coronary heart disease.[16] Importantly, poor sleep has been associated with increases in obesity, diabetes, and hypertension, all of which are strong predictors of future development of CVD.[17-20] However, the ability to accurately predict risk of CVD based on these traditional risk

factors (obesity, diabetes, and hypertension) appears to weaken with increasing age.[21] Therefore, research to identify novel risk factors (e.g. sleep quantity and quality) associated with cardiovascular outcomes is especially important in the elderly.

Atherosclerosis in the carotid arteries is a marker of generalized atherosclerosis.[22] Carotid intima-media thickness (CIMT), the distance between the interfaces of the lumen-intima and the media-adventitia boundaries, is a surrogate marker of atherosclerosis.[23-28] Larger CIMT is due to the accumulation of lipid, smooth muscle cells and inflammatory infiltrate that are part of the atherosclerotic process.[29] In this regard, a higher CIMT is associated with CVD risk factors such as higher age, body mass index (BMI), and cholesterol levels, male gender and the presence of diabetes, hypertension, and smoking. Moreover, CIMT has been shown to be a strong predictor of future cardiovascular disease and events.[24-28]

Literature on sleep duration and quality and the relationship with subclinical carotid atherosclerosis is limited. In the first of only three known studies that investigated the relationship between sleep and CIMT, Wolff et al. reported that both short (5 hours) and long (11 to 12 hours) self-reported total (night and day) sleep durations were associated with greater CIMT in a large (n=2,437) cross-sectional analysis.[30] The second study reported no association between self-reported insomnia (defined as difficulty falling asleep, maintaining sleep, and early morning awakening) and CIMT in a population-based cohort study of 1,605 participants with a mean age of 65 years.[31] The third and most recent cross-sectional analysis on 2,214 men and women over the age of 40 years indicated that long self-reported sleep (≥7 hours) was associated

with a greater risk of CIMT ≥1.2mm compared with a sleep duration of 6 hours (OR, 1.26; 95%CI, 1.03-1.54).[32]

While evidence supporting a link between insufficient sleep and arterial disease is accumulating, data on objectively measured sleep and cardiovascular risk factors in older adults is limited and conflicting.[14, 33-36] Research examining these associations in elderly dementia caregivers is even more limited, yet this group generally experiences frequent sleep difficulties, thereby providing greater opportunity for sleep to impact health.[36] Therefore, the purpose of this cross-sectional analysis was to examine whether objectively measured sleep quantity and disturbed sleep were associated with atherosclerosis in the carotid arteries from ultrasound imaging among 126 community-dwelling elderly spousal Alzheimer's caregivers who participated in the Alzheimer Caregiver Coping Study. Since pathologic processes related to atherosclerosis can be promoted by the physiologic responses to insufficient sleep, it was hypothesized that chronically inadequate sleep duration and disturbed sleep increase the possibility for arterial damage and downstream cardiovascular disease.

Methods

The Alzheimer Caregiver Coping Study

The Alzheimer Caregiver Coping Study was conducted at the University of California, San Diego (UCSD) to examine the relationships between physiological and psychological stress markers, and health risk factors in spousal Alzheimer's caregivers. All data was collected between 2007 and 2010.

Participants were 126 community-dwelling men and women over the age of 55 years who were married, living with, and providing continuous in-home care to a spouse

diagnosed with Alzheimer's disease. Caregivers were recruited via referrals from the UCSD Alzheimer's Disease Research Center, community Alzheimer caregiver support groups, local agencies serving caregivers, recommendations from other participants enrolled in the study, flyers, media advertisements, and senior health fairs. Participants provided written informed consent, and the study was approved by the UCSD Institutional Review Board.

Caregivers were excluded if they had a current diagnosis or treatment for a life-threatening or terminal medical condition that required ongoing care (i.e. advanced CVD, Parkinson's disease, and/or a severe psychiatric disorder), extreme hypertension (>200/120 mm Hg), current or recent (within the past 5 years) treatment for cancer, organ transplantation requiring anti-rejection medication, or use of corticosteroids, β-blocking, and/or anticoagulant medication.

Measures

All measurements and assessments, other than objective measures of sleep, were administered between 9:00AM and 11:00AM in participants' homes by trained research personnel, which included a nurse, research assistant, and certified sonographer. The research assistant administered a semi-structured interview that gathered information on sociodemographics, years of caregiving, psychosocial functioning, caregiving overload, health behaviors, medical history, hospitalizations, and alcohol/drug history. Fasting venous blood was drawn within one week of the initial visit between 9:00AM and 11:00AM.

Sociodemographics, Medical Data, and Past Health History

Sociodemographic information such as age, gender, education, and occupation were collected by interview. History of cardiovascular disease was defined as previous heart attack, heart failure, angina, heart disease, stroke, or transient ischemic attack. Caregivers were asked if they had ever been told by a physician that they had type 2 diabetes, hypertension, dyslipidemia, myocardial infarction or stroke, with answers coded yes/no. Information about cardiovascular medication (i.e., aspirin, angiotensin-converting enzyme inhibitors, and statins) and antidepressant use (i.e., atypicals, selective serotonin reuptake inhibitors, tricyclics, etc.) was obtained via participant report and confirmed by examination of the medication containers. Smoking status, alcohol consumption, and physical activity information was also collected during the home visit.

Smoking status was categorized as current/former smoker vs. never smoker and also measured in terms of years of smoking. Alcohol consumption was quantified in terms of the number of alcoholic drinks consumed per week. Data on height and weight were obtained by participant report, and body mass index (BMI) was calculated as the ratio of self-reported weight in kilograms to height in meters squared. Participants with a BMI > 30 were classified as obese. Blood pressure was measured three times using a non-invasive Microlife BP monitor (model number 3AC1-1PC) with the caregiver in a supine position. The average of the three measurements was used to create a composite resting blood pressure estimate. Hypertension was defined either by self-report of physician-diagnosed hypertension and current use of a prescription antihypertensive, or as a resting diastolic blood pressure or systolic blood pressure ≥90 or ≥140 mmHg, respectively. Dyslipidemia was defined either by total-to-HDL ratio >5, or by self-report of current use of prescription cholesterol-lowering medications. Diabetes was defined

either by self-report of physician-diagnosed diabetes and current use of antiglycemic medication, or a fasting blood glucose ≥126 mg/dL, as classified by the American Diabetes Association.[37]

Psychological Questionnaires

The semi-structured interview included questions that evaluated duration of caregiving, psychological distress, perceived stress, depressive symptom severity, and anxiety and depressive symptoms. Duration of caregiving was determined by reported time in years that had elapsed since the spouse was diagnosed with Alzheimer's disease. The 10-item short form of the Center for Epidemiologic Studies Depression Scale (CESD-10) was used to assess depressive symptoms.[38-40] Levels of life stress were assessed with the 4-item Role Overload Scale, a self-report 4-point Likert scale ranging from 1=not at all to 4=completely, which measured the extent to which participants felt overwhelmed by everyday tasks. Lower role overload and CESD-10 scores indicate lower stress and depressive symptoms, respectively. Reliability (Cronbach's alpha) for the 4-item Role Overload Scale has ranged from 0.71 to 0.77 in different samples of elderly caregivers,[41] however in our sample, the alpha coefficient is 0.82. Cronbach's alpha for the CESD-10 in our sample of caregivers is 0.52.

Objective Sleep Measure

Objective sleep/wake activity was measured with the Actiwatch-Light® (Mini Mitter Co., Inc, a Respironics, Inc. Co., Bend, OR), which was worn for 72 consecutive hours (three consecutive 24-hour periods) on participants' non-dominant wrist. Actigraphy has been validated in and recommended for use among elderly populations and has been compared favorably with polysomnography (PSG), which is deemed the

gold standard for sleep assessment.[42, 43] The Actiwatch-Light® uses a piezoelectric linear accelerometer (sensitivity <.01 g-force) with a sampling rate of 32Hz to measure and record wrist movement. Movement, which was measured as the number of accelerations per minute, was captured via internal motion sensors in the watch. Calculating wrist activity over time allowed for an objective measure of duration and disruption of sleep. The recorded actigraphy data were analyzed using Actiware® sleep and activity monitoring software (version 5, by Mini Mitter|Respironics/Philips). Sleep diaries completed by participants estimated times the actigraphy watch was removed, bedtimes, and wake times and were used for editing the actigraphy data.

The following sleep parameters used in the present analysis were averaged across the three consecutive 24-hour time periods and selected a priori: 1) total nighttime sleep duration (hours per night spent sleeping from reported bedtime to final uptime); 2) total hours of daytime sleep (nap time), with naps defined as no activity for a minimum of 10 minutes; and 3) hours awake after sleep onset (WASO) between reported bedtime and final uptime, which was used to denote sleep disturbance.

Outcomes – Ultrasound Imaging of Carotid Artery Intima-Media Thickness

Carotid artery ultrasound was conducted with the participant lying in the supine position, using an Acuson Cypress Portable Ultrasound Unit with a 5.4-6.6 MHz Acuson 7L3 transducer. High resolution B-mode ultrasound images were taken of the near and far walls of the common carotid artery section from two uniform interrogation angles per vessel (left: 180° and 240°; right: 120° and 180°). Segments were defined by the carotid flow divider, which was used as a reference point: the common carotid was defined as

the segment 1 to 2 cm proximal to the flow divider. Imaging of all participants was conducted by the same certified sonographer to avoid inter-sonographer inconsistency.

The computer program Vascular Research Tools (Medical Imaging Applications, Coralville, IA) was used to analyze carotid intima-media thickness (CIMT) by a blinded image reader. Carotid intima-media thickness (mm) was defined as the distance between the lumen-intima boundary and the media-adventitia boundary. The mean of the means measured from the far walls of the common carotid artery segment, which will be referred to as the "common CIMT", was examined in the current study.

Statistical Analysis

Associations between continuous sleep measures, key covariates (e.g. hypertension), and CIMT were tested using Pearson *r* and t-tests, and potential confounders were identified. First, the sleep variables were treated as continuous. In secondary analyses, to test for non-linear associations or thresholds, sleep parameters were modeled categorically by combining sleep parameters into three new variables: 1) nighttime sleep duration *with* daytime sleep duration; 2) nighttime sleep duration *with* WASO; and 3) daytime sleep duration *with* WASO. In these secondary analyses, reference groups were chosen based on current viewpoints about clinically significant cut points of these sleep parameters in elderly adults, and daytime sleep duration was reported in minutes for ease of interpretation. Specifically, 7-8 hours of sleep at night, <1 hour of WASO at night, and <30 minutes of daytime sleep are generally considered the normal cut-offs for elderly adults, and were therefore used as the reference groups and/or cut points.[42, 44, 45]

Multivariable linear regression analysis was employed to identify which objectively measured sleep parameters were significantly associated with CIMT independent of covariates. To reduce risk of over-fitting in the multiple regression models, covariates were restricted to age, gender, those variables showing significant ($p<0.10$) univariate correlations with the exposure variables (sleep parameters) or the outcome variable (the subclinical atherosclerotic marker), and variables selected a-priori likely to be related to atherosclerosis and sleep. Covariates adjusted for in the first model (Model 1) included age and gender. The second multivariable model (Model 2) included the covariates from Model 1 plus education, BMI, physical activity, smoking, hypertension, diabetes, dyslipidemia, and history of CVD. In the third model (Model 3), covariates from Model 2 were included plus role overload and depression (CESD-10) scores. An alpha level of $p<0.05$ (2-tailed) was used to indicate statistical significance, and all statistical analyses were conducted using SPSS version 16.0 statistical package.

Results

Participant Characteristics

Demographic and health characteristics for the sample of elderly Alzheimer's caregivers are presented in Table 4.1. Caregivers were a mean age of 74 years, primarily women (71%), Caucasian (92%), slightly overweight, and had been providing care for an average of 4.3 years. The majority of caregivers had hypertension (81%) and dyslipidemia (62%), while 19% were found to have Type 2 diabetes, and 20% had a history of cardiovascular disease. On average, caregivers obtained 7 hours and 20 minutes of sleep and 1 hour of WASO at night, and 48 minutes of sleep during the day.

Continuous Sleep Variables and Carotid Intima-Media Thickness

In unadjusted analyses, WASO was significantly positively correlated with mean common CIMT (p=0.01). As shown in Table 4.2, in all 3 adjusted models WASO was still positively associated with mean common CIMT (Model 1: B=0.05, p=0.02; Model 2: B=0.04, p=0.04; Model 3: B=0.04, p=0.05). Similarly, daytime sleep duration was significantly and inversely associated with mean common CIMT in all 3 adjusted models (Model 1: B=-0.03, p=0.05; Model 2: B=-0.03, p=0.04; Model 3: B=-0.04, p=0.02). Specifically, when adjusting for covariates related to sleep and atherosclerosis, for every additional hour of sleep obtained during the day, mean common CIMT decreased by 0.04mm, and for every additional hour of WASO, mean common CIMT increased by 0.04mm. With regard to covariates, greater mean common CIMT was significantly correlated with increasing age, diabetes and hypertension ($p<0.05$ for all).

Combined Sleep Parameters and Carotid Intima-Media Thickness

Associations between combined sleep parameters and CIMT were examined. As shown in Figure 4.1, when adjusting for covariates included in Models 2 and 3, caregivers who obtained <30 minutes of daytime sleep *and* ≥1 hour of WASO had significantly greater mean common CIMT compared to caregivers who obtained <30 minutes of daytime sleep *and* <1 hour of WASO (reference group) (B=0.07 and B=0.06, respectively; $p<0.05$ for both). Conversely, as shown in Figures 4.2 and 4.3, CIMT did not significantly differ by combined nighttime *and* daytime sleep duration groups, or by combined nighttime sleep duration *and* WASO groups, respectively.

Discussion

Primary results from this analysis on elderly, community-dwelling Alzheimer's caregivers indicate that longer time spent napping was associated with significantly

reduced mean common CIMT, while longer WASO was associated with significantly increased mean common CIMT. After adjusting for covariates related to sleep and atherosclerosis, for every additional hour of naptime during the day, mean common CIMT decreased by 0.04mm, while for every additional hour of WASO, mean common CIMT increased by 0.04mm. These numbers are relevant, as a reduction in CIMT by 0.1mm among patients with a CIMT equal to 1.2mm, who are generally considered to have carotid artery atherosclerosis, would classify them as free of atherosclerosis in the carotid arteries.[27, 32] Furthermore, a meta-analysis on data from 37,187 participants indicated that a CIMT difference of only 0.1mm increased future risk of myocardial infarction and stroke by 10-15% and 15-18%, respectively.[27]

Our results also indicated that caregivers who napped <30 minutes during the day *and* had ≥1 hour of WASO had significantly greater mean common CIMT compared to caregivers who napped <30 minutes *and* had <1 hour of WASO. This relationship appeared to be driven primarily by WASO. Therefore, our secondary analyses with combined sleep groups support findings from the primary analyses that suggest an association between WASO and carotid intima-media thickness.

To our knowledge, there are no studies that have investigated the relationship between objectively measured nighttime sleep disturbance and carotid artery atherosclerosis. However, our finding that WASO was significantly positively associated with mean common CIMT is supported by previous studies reporting that disturbed sleep increases risk of cardiovascular morbidity.[12, 27, 46, 47] For example, data from the Whitehall II Study, a large (n=10,308) longitudinal cohort study on men and women,

indicated that self-reported sleep disturbance significantly increased risk of coronary heart disease 15 years later.[12, 48]

Our results that suggest an association between longer naps and reduced common carotid intima-media thickness are intriguing in the face of current literature that indicates associations between longer naps and increased BMI, risk of type 2 diabetes, and mortality.[49-53] However, since blood pressure, which predicts carotid IMT, acutely declines during daytime sleep, perhaps less nap time during the day leads to raised blood pressure, in turn increasing carotid intima-media thickness.[32, 54-56] In other words, in a population of caregivers exposed to chronic stress, longer naps could provide for greater periods of reduced blood pressure, which may be protective against thickening of the carotid intima-media.[57] It can be hypothesized that frequent periods of this acute reduction in blood pressure during a nap may be one feature explaining the reduced mean common CIMT that was found in these elderly Alzheimer's caregivers.

Additionally, our findings that nap duration was inversely associated with mean common CIMT are supported by data from a large (n=23,681) population-based cohort study by Naska et al., which indicated an inverse relationship between self-reported nap times and risk of coronary mortality when controlling for confounders.[51] Individuals in the Naska et al. study who napped routinely had a 37% reduced risk of coronary mortality compared to non-nappers.[51] Another study by Kalandidi et al. that reported a negative association between self-reported nap duration and risk of CHD in a case-control study (n=899) also supports our findings.[58] Contradicting our results, analyses from a large (n=4,797) study on adults over the age of 45 years indicated that longer self-reported daytime naps were associated with worse measures of subclinical atherosclerosis, but

coronary artery calcium rather than CIMT was used as the marker for subclinical atherosclerosis.[59]

It is important to note that naps were estimated from wrist actigraphy in our study. While nighttime sleep recorded by actigraphy has been validated against the gold standard PSG, daytime napping has not. We defined naps as a minimum of 10 minutes with no movement, as it is unlikely that an individual could be still for that long unless asleep. Nevertheless, it is possible that the nap computations based on actigraphy are less accurate than naps recorded with PSG. Since it is extremely difficult to measure 24-hour sleep polysomnographically, actigraphy at this time is still the best estimate or proxy.

Sleep-related atherosclerotic progression may be a potential avenue through which caregiving could predispose increased risk for CVD. Our results support findings from prior analyses[12, 15, 16] that indicated associations of sleep duration and disturbed sleep with increased risk of cardiovascular disease by specifically unearthing an inverse correlation between napping and CIMT, and a positive association between WASO and CIMT in elderly Alzheimer's caregivers. However, since the mechanisms that may mediate the presumed relationships of both sleep quantity and disturbed sleep with subclinical atherosclerosis remains to be established, further research on associations between objectively measured sleep and subclinical atherosclerosis in older participants is warranted.

Limitations

Due to the cross-sectional design of the study, inferences regarding causality or directionality of associations between the sleep parameters and subclinical marker of atherosclerosis cannot be established. Since data on obstructive sleep apnea and snoring

were unavailable, we were not able to adjust for this syndrome or distinguish between sleep loss due to spousal or environmental disturbances, or other pathological conditions that might disrupt sleep.[60, 61] It is possible that napping and disturbed nighttime sleep could be indicative of and exacerbated by sleep apnea, respectively. The caregivers in our sample had less disturbed sleep than has been observed in previous studies, they were not considered sleep deprived, and there was limited variance in the sleep variables.[44, 62] Therefore, if the caregivers had in fact had inadequate or disturbed sleep, there may have been greater opportunity for the insufficient sleep to contribute to subclinical atherosclerotic progression, potentially resulting in stronger associations between the sleep and CIMT measures.

Conclusions

The current findings suggest that more disturbed nighttime sleep (WASO) and shorter daytime naps were associated with increased carotid intima-media thickness in this sample of elderly Alzheimer's caregivers. These findings provide additional information from which future prospective studies and interventions could examine whether sleep effects atherosclerotic progression over time in caregivers. Limited physical activity, poor diet, smoking, excessive alcohol consumption, and genetics certainly play an important role in the progression of atherosclerosis; but insufficient sleep, which is increasingly recognized as a modifiable risk factor and major public health concern, could also contribute.[35, 50, 63-65] A more complete theoretical model of the etiology of carotid artery IMT progression that includes sleep ought to be considered in future studies. If the hypothesized relationships are born out, this model could offer valid, directionally-oriented physiologic mechanisms that link sleep to these measures of

subclinical atherosclerosis. Understanding these physiologic mechanisms that connect sleep quantity and quality to subclinical atherosclerosis has the potential to aid practitioners in the prevention and management of prevalent and escalating problems associated with cardiovascular risk factors and CVD.

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Table 4.1. Characteristics of a sample of elderly Alzheimer's caregivers (N=126) in a study of the associations of sleep with subclinical atherosclerosis	
Age (years), mean (SD)	74.16 (7.98)
Female, n (%)	89 (71.20)
Ethnicity, n (%)	
Caucasian	115 (92.00)
Non-Caucasian	10 (8.00)
Education (years), mean (SD)	15.15 (3.05)
Body mass index (kg/m^2), mean (SD)	26.49 (4.71)
Systolic blood pressure (mmHg), mean (SD)	134.3 (15.3)
Diastolic blood pressure (mmHg), mean (SD)	75.8 (8.6)
Blood glucose (mg/dL), mean (SD)	105.1 (43.7)
History of cardiovascular disease, n (%)[1]	25 (19.84)
Duration of caregiving (years), mean (SD)	4.33 (3.38)
Hypertension, n (%)	99 (80.50)
Dyslipidemia, n (%)	74 (61.70)
Type 2 diabetes, n (%)	23 (19.17)
Health Behaviors	
Ever smoker, n (%)	58 (46.03)
Alcohol consumption (drinks/week), mean (SD)	1.40 (1.46)
Meets CDC physical activity recommendation, n (%)[2]	42 (33.30)
Psychological Variables	
Role Overload score, mean (SD)	5.18 (3.15)
CESD-10 score, mean (SD)	8.78 (5.81)
Medication Use	
Current use of antidepressants, n (%)	32 (25.40)
Current use of cholesterol-lowering medication, n (%)	57 (45.20)
Current use of high blood pressure medication, n (%)	76 (60.30)
Current use of diabetes medication, n (%)	15 (11.90)
Objective Sleep Variables	
Nighttime sleep duration (hours), mean (SD)	7.32 (1.12)
Daytime sleep duration (hours), mean (SD)	0.79 (0.67)
Nighttime WASO (hours), mean (SD)	1.04 (0.45)
Subclinical Marker of Atherosclerosis	
Mean common CIMT in millimeters, mean (SD)	0.72 (0.11)

WASO, wake after sleep onset.
[1]Includes heart attack, heart failure, angina, heart disease, and stroke or transient ischemic attack.
[2]Engages in ≥30 minutes of moderate intensity physical activity on 5 or more days of the week.

Table 4.2. Sleep parameters as predictors of carotid intima-media thickness in a sample of elderly Alzheimer's caregivers (N=126), adjusting for covariates

		Mean Common CIMT
		B (95% CI)
Nighttime sleep duration (hours)	Model 1	-0.01 (-0.03, 0.01)
	Model 2	-0.01 (-0.03, 0.01)
	Model 3	-0.01 (-0.03, 0.01)
Daytime sleep duration (hours)	Model 1	-0.03 (-0.06, 0.00)*
	Model 2	-0.03 (-0.06, -0.001)*
	Model 3	-0.04 (-0.07, -0.01)*
Nighttime WASO (hours)	Model 1	0.05 (0.01, 0.09)*
	Model 2	0.04 (0.003, 0.08)*
	Model 3	0.04 (0.001, 0.08)*

Model 1 – Adjusted for age and gender.
Model 2 – Adjusted for variables in Model 1 + education, BMI, physical activity, smoking, hypertension, dyslipidemia, diabetes, and history of CVD.
Model 3 – Adjusted for variables in Model 2 + Role Overload and depression (CESD-10) scores.
*$p \leq 0.05$
WASO, wake after sleep onset.

Figure Legend

Figure 4.1. Associations of combined daytime sleep duration and nighttime WASO groups with common carotid intima-media thickness in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates.

Figure 4.2. Associations of combined nighttime and daytime sleep duration groups with common carotid intima-media thickness in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates.

Figure 4.3. Associations of combined nighttime sleep duration and nighttime WASO groups with common carotid intima-media thickness in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates.

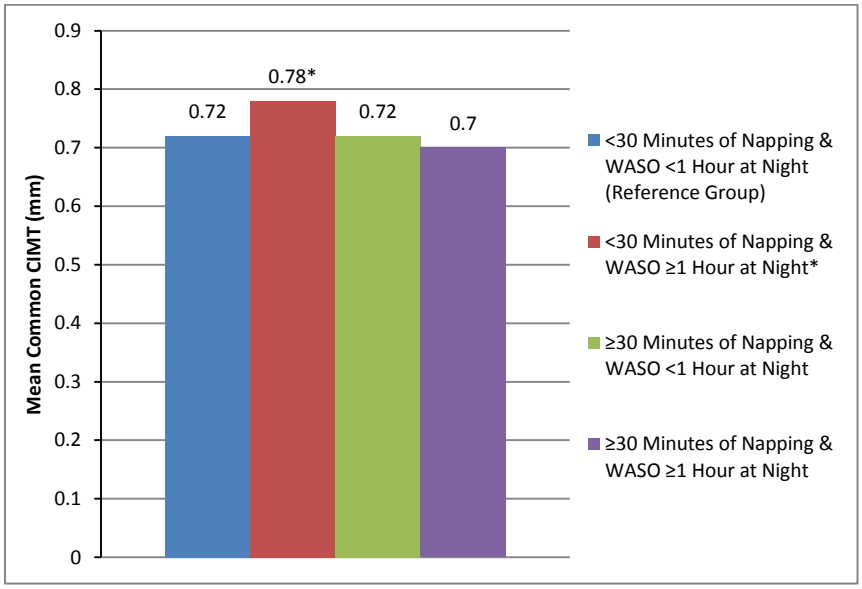

Figure 4.1. Associations of combined daytime sleep duration and nighttime WASO groups with mean common carotid intima-media thickness in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates.

*Adjusting for covariates in Model 3, caregivers who obtained <30 minutes of daytime sleep *and* ≥1 hour of WASO had significantly greater (p=0.04) mean common CIMT compared to the reference group.

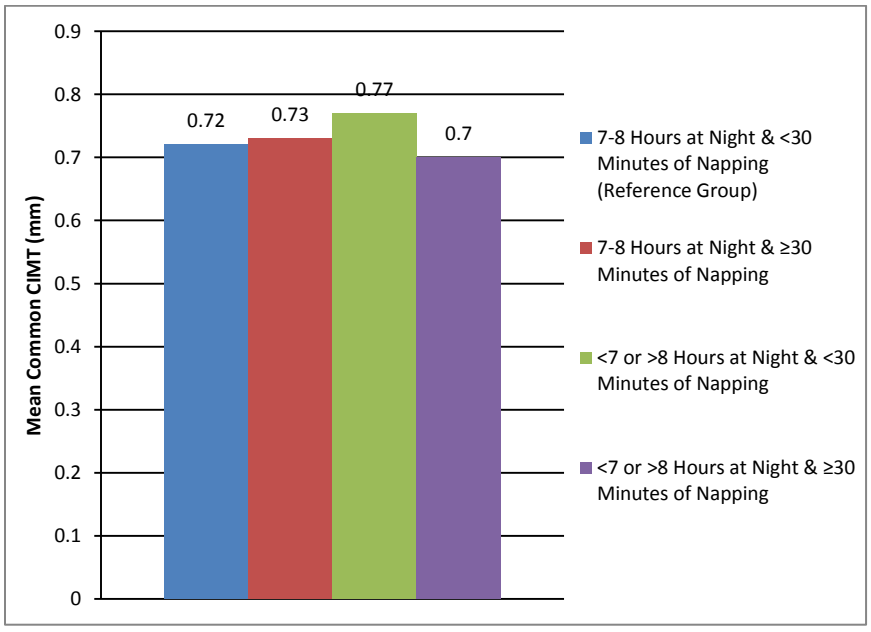

Figure 4.2. Associations of combined nighttime and daytime sleep duration groups with common carotid intima-media thickness in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates.

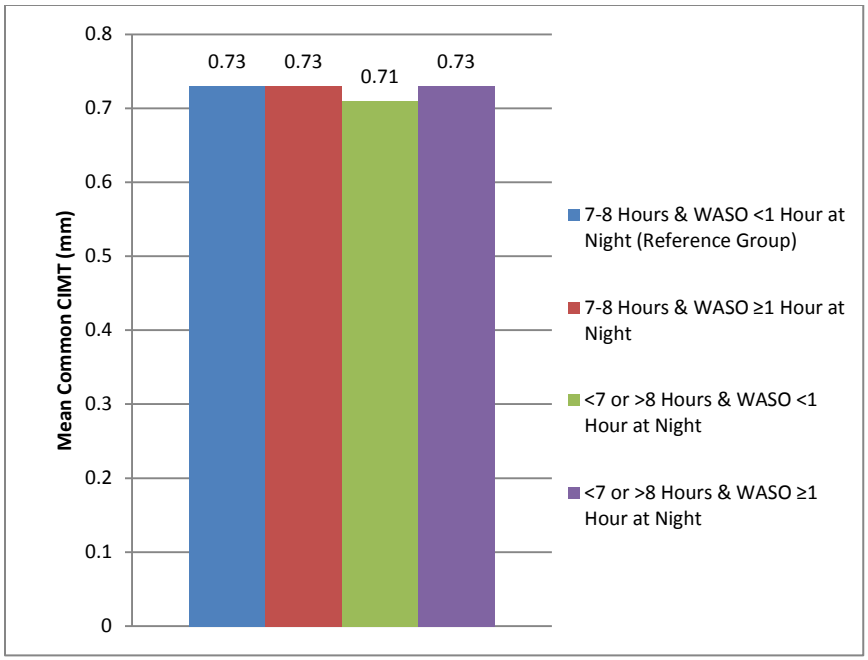

Figure 4.3. Associations of combined nighttime sleep duration and nighttime WASO groups with common carotid intima-media thickness in a sample of elderly Alzheimer's caregivers (N=126), adjusted for covariates.

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CHAPTER 5: Discussion

Summary of Results

Analyses presented in these three manuscripts suggest that, in a sample of community-dwelling elderly Alzheimer's caregivers, objectively measured nighttime sleep duration and efficiency were positively associated with morning plasma catecholamine concentrations (Chapter 3), while more disturbed nighttime sleep and shorter naps were associated with increased subclinical atherosclerosis in the carotid arteries (Chapter 4). However, significant associations between the sleep parameters and prevalence of type 2 diabetes, dyslipidemia, or hypertension in these caregivers were not found (Chapter 2). These findings are illustrated in Figure 5.1 (page108), which presents hypothesized pathways linking insufficient nighttime sleep and short napping with their significantly associated markers of CVD risk (plasma catecholamine concentrations and common carotid intima-media thickness) in elderly Alzheimer's caregivers.

Significance

Findings presented in Chapter 2 indicate that objectively measured sleep was not significantly associated with prevalent type 2 diabetes, hypertension or dyslipidemia in a sample of elderly Alzheimer's caregivers. However, the small sample size of caregivers may have limited our ability to detect significant associations between the sleep parameters and metabolic conditions, as the majority of the associations were in the hypothesized direction. While these findings contradict most published data indicating significant associations between sleep and diabetes,[1-3] they are consistent with studies suggesting no significant associations between sleep and risk of hypertension or lipid-lipoprotein concentrations in older participants.[4, 5] It is possible that relationships

between sleep and metabolic conditions become less apparent with age.[5-9] A cross-sectional study by Kim et al. supports this hypothesis, as data indicated that among adults <65 years old, risk of hypertension was significantly greater in those who reported sleeping ≤5 hours per night on average compared to those who reported sleeping 7 hours per night on average; yet among adults ≥65 years old, self-reported nighttime sleep duration was not significantly associated with risk of hypertension.[6]

Analyses presented in Chapter 3 suggesting that longer and more efficient nighttime sleep were associated with higher concentrations of morning plasma catecholamines in a sample of elderly caregivers are difficult to explain, as they contradict published studies indicating a positive association between sleep disturbance and plasma epinephrine and norepinephrine concentrations.[10, 11] However, due to dissimilar research methods and participant characteristics, we cannot readily compare our results with published data.[10-13] Furthermore, to our knowledge no studies have examined associations between sleep and plasma dopamine. Thus, heightened catecholamine activity may benefit cardiovascular health in elderly individuals.[14, 15] As shown in Figure 5.1, reduced plasma dopamine concentrations may lead to: 1) increased platelet aggregation;[16] 2) increased blood pressure;[17, 18] 3) reduced glucose tolerance and regulation;[17] and 4) increased inflammation.[19] These proposed pathways are based on known actions of plasma dopamine, as described in detail in Chapter 3.[20, 21] Therefore, chronically insufficient sleep in elderly caregivers may alter plasma catecholamine concentrations in the opposite direction from previously held notions, which in turn may mediate the relationship between insufficient sleep and adverse cardiovascular outcomes.

As presented in Chapter 4, analyses indicate that more disturbed nighttime sleep and shorter naps were associated with increased subclinical atherosclerosis in the carotid arteries in a sample of elderly Alzheimer's caregivers. To our knowledge, no studies have investigated the relationship between objectively measured sleep disturbance and carotid artery atherosclerosis. However, our finding that sleep disturbance was significantly associated with higher mean common CIMT supports previous data indicating that disturbed sleep increases risk of cardiovascular morbidity.[22-26] Alternatively, our results that suggest an association between longer naps and reduced CIMT are intriguing and potentially provocative in the face of current conflicting literature on the health effects of daytime sleep in older adults.[1, 27-30] Nonetheless, our results are supported by data from two large studies by Kalandidi et al. and Naska et al., which indicated inverse relationships between self-reported nap time and risk of coronary heart disease and coronary mortality, respectively.[28, 31] Since blood pressure, which predicts CIMT, declines during naps, longer daytime sleep may provide for slightly lower blood pressure throughout the day, in turn protecting against carotid intima-media thickening.[32-35] Therefore, as illustrated in Figure 5.1, shorter naps accompanied by shorter periods of blood pressure reduction could help explain the inverse association between nap duration and CIMT that was found.[36] The current analyses suggest that napping in elderly caregivers may be beneficial for cardiovascular health, and atherosclerotic progression related to disturbed or short sleep could be one mechanism predisposing them to increased risk for CVD.

Limitations and Strengths

The caregivers in our sample experienced less disturbed sleep than that observed in previous studies, they were not considered sleep deprived, and limited variance in the sleep variables was noted.[37, 38] Additional studies involving caregivers experiencing more disturbed or inadequate sleep may reveal further progression of CVD risk markers and perhaps stronger associations between the sleep parameters and outcomes of interest. Due to the cross-sectional design of the study, inferences regarding causality or directionality of associations between the sleep variables and markers of CVD risk cannot be established. Also, nap durations estimated from wrist actigraphy, unlike nighttime sleep, have not been validated against the gold standard in the field (i.e. polysomnography) so it is possible that the nap computations based on actigraphy are less accurate than naps measured by polysomnography. However, actigraphy provides the best estimate at this time, as it is difficult to measure 24-hour sleep polysomnographically. Lastly, the small sample size may have limited power of the analyses to detect significant associations between the sleep parameters and prevalent metabolic conditions, as presented in Chapter 2.

These analyses provide additional relevant information on the relationships between sleep and markers of CVD risk in elderly caregivers. Specifically, our study used three days/nights of actigraphy to objectively and non-invasively measure sleep in participants' homes, while previous sleep studies often based sleep measurements on one night of polysomnography or self-report.[27, 39-42] One night of polysomnography may not be representative of habitual sleep, and self-reported sleep measures are less reliable than objective measurements.[43-46] Additionally, to our knowledge these are the first analyses that 1) investigated associations between sleep and plasma dopamine; and 2) examined

relationships of combined sleep quantity *and* quality parameters with markers of CVD risk in elderly adults.

Conclusions

While findings in the three manuscripts suggest that sleep was not significantly associated with prevalence of metabolic conditions, sufficient nighttime sleep and/or napping were associated with increased morning plasma catecholamine concentrations and reduced subclinical atherosclerosis in the carotid arteries in a sample of elderly Alzheimer's caregivers. Limited physical activity, poor diet, smoking, excessive alcohol consumption, and genetics certainly play an important role in the progression of CVD risk markers; but insufficient sleep, a modifiable risk factor and major public health concern, likely contributes.[1, 46-49] Experimental studies with larger samples and non-invasive, objective sleep measures that aim to extend and/or improve sleep are warranted to examine whether metabolic conditions are improved, plasma catecholamine concentrations are altered, and atherosclerotic progression is slowed in elderly adults, and in turn, whether downstream harmful CVD outcomes are reduced.

As sufficient sleep is a vital component of a healthy lifestyle, future studies of the etiology of CVD progression in the elderly ought to utilize a comprehensive theoretical model that includes sleep. If the hypothesized relationships are borne out, this model could demonstrate valid, directionally-oriented physiologic mechanisms that link sleep to risk for CVD, which in turn could aid practitioners in the prevention and management of CVD risk factors and downstream disease in elderly adults.

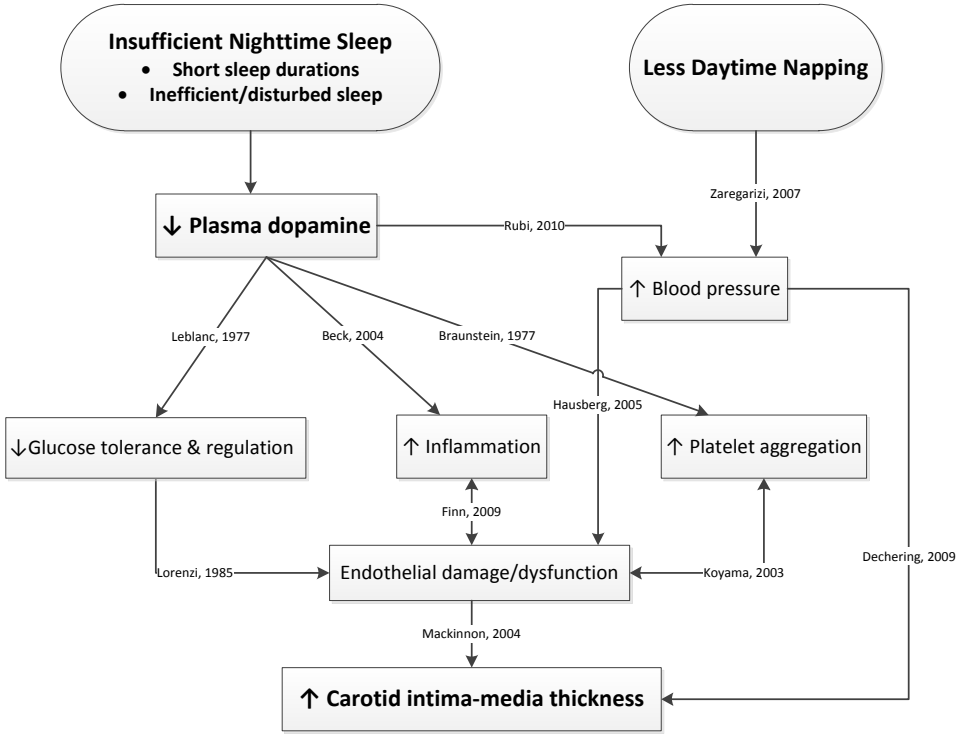

Figure 5.1. Theoretical Model: Potential pathways linking insufficient nighttime sleep and short daytime napping with significantly associated outcomes (**bolded**) in a sample of elderly Alzheimer's caregivers.

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APPENDICES

Appendix 1: Protection of Human Subjects

Human subjects research protocols were submitted and approved by the University of California, San Diego Institutional Review Board. Key sections of the protocol are included below.

Potential Risks to Subjects

Potential risks are minimal. The protocol involves time commitment over a period of several days. The rating scales and questionnaires are fairly innocuous. The volume of blood to be taken during the stressor protocol is approximately 110 ml at each annual assessment. This volume is well below the accepted maximum allowed by UCSD Human Subjects guideline. Nevertheless, we will screen the participants for a normal hematocrit prior to removing this volume of blood. Blood sampling carries a minimal possibility of infection. We will use standard precautions in protecting the puncture site. All blood drawing procedures will be performed by a registered nurse. The major physical discomfort for these protocols is that of venipuncture. During arterial occlusion (preventing blood flow from the heart from flowing to arm) there may be mild discomfort such as tingling, numbness, or throbbing in the fingers. These symptoms will disappear within one minute after the cuff is deflated. Participants may develop flushing and headache transiently in response to the nitroglycercine sublingual tablet. The risks associated with having sleep recorded include possible skin irritation at the site of the EEG, chin EMG, and EOG electrodes. Care is taken to minimize irritation by using special electrode gel. There are no risks associated with actigraphy.

Risk Management Procedures

We reduce burden of participating in the study by conducting evaluations in the participant's home (unless the participant prefers to come to our lab). This reduces time spent by participants in travel, and obviates need for finding an alternative care provider for the demented spouse. Protection of participant confidentiality and privacy will be rigorously guarded by assignment of coded numbers to each file for both forms and computer databases. Keys to these codes will be stored in a locked file cabinet in the Alzheimer Caregiver Project office. The dangers of adverse effects of blood drawing are minimal as noted above.

Echo measurements of the carotid and brachial artery are very low risk. If we find evidence for high-grade obstruction of the carotid artery in a caregiver, that person will be referred for formal evaluation of their carotid artery. Occlusion of the brachial artery with a blood pressure cuff is low risk. Nevertheless, persons with known or suspected vascular disease of the arm, lymphedema of the arm or any condition that might be exacerbated by a blood pressure cuff will not have the procedure performed.

Participants will be given a single sublingual tablet of nitroglycerin. No participant with low blood pressure (<100/60) or taking a drug such as a phospodiesteras

inhibitor that might adversely interact with nitroglycerin will be given a tablet of the medicine. Participants will remain supine after receiving nitroglycerin long enough for its effects to fully dissipate before being instructed that they may arise.

FREEDOM TO WITHDRAW WITHOUT PREJUDICE: Participation in this project is completely voluntary. A participant's decision to participate will not prejudice them or their medical care. Also, participants are free to withdraw consent at any time without prejudice. Again, PARTICIPATION IN THIS STUDY IS ENTIRELY VOLUNTARY.

CONFIDENTIALITY: Answers to all questions will be kept strictly confidential. All of these data will be coded by number only so that anonymity is preserved. Data will be available only to the investigators and the staff associated with this project. Any data that may be published in scientific journals will not reveal the identity of the participants. In the interest of public safety, information about patients may be provided to Federal ad regulatory agencies as required. The Food and Drug Administration, for example, may inspect records and learn participants' identity if this study falls within its jurisdiction. In addition, if participants provide us with information that indicates they are a danger to themselves or others, or if they are a victim of abuse, we are required by law to contact the appropriate agencies or authorities. In all written reports provided to the National Institute on Aging, which is the funding source, no identifying information will be revealed.

INVITATION TO QUESTION: If participants have any questions, they will have adequate opportunity to ask us by calling Dr. Igor Grant or members of his staff at (858) 534-3495.

DATA SAFETY: Data safety will be of utmost importance in this project. Data will be coded by subject number only and will be filed in locked file cabinets in locked staff offices. In addition, signed consent forms will be filed in a separate location from the raw data. A codebook linking subject identifying information with subject number will be kept on a computer that is password protected and, within that, a file that is password protected. Data will be entered twice independently and discrepancies will be resolved by checking raw data.

Adverse events in this research project are expected to be extremely rare. However, we have established a plan for resolving any adverse event should one occur. First, during screening for the project, trained research personnel will assess for any serious medical or psychological conditions that may require immediate medical attention or psychiatric treatment (using standardized screening tools, such as the CES-D self-report scale to assess depressive symptoms. This is because the presence of serious medical or psychiatric conditions would make these individuals inappropriate for the proposed research study. Should attention be required, staff will provide these individuals with information about suitable referrals, including local hospitals, clinics, and/or relevant health-care and mental health professionals, and they will strongly encourage the individual to follow up with these referrals.

Potential Benefits

We do not anticipate that individual subjects will receive much benefit from the stress protocol data that are gathered, however, for the field, we should be able to improve our understanding of how the stress of caregiving impacts the cardiovascular system of these individuals.

Risk/Benefit Ratio

Risks of this research are slight and the benefits to the participant are judged as minimal. Participants may find questions somewhat distressing, however our experience indicates that they enjoy the company of our staff, and talking to someone about their problems relieves some stress. Participants will also have sleep assessments that might provide clinically relevant information. We judge that the importance of the knowledge resulting from this study will be significant, therefore, the risk to benefit ratio is low.

Payment for Participation

Participants will receive $100.00 at each yearly visit involving the stress interview and blood draws. Note that participants will not be reimbursed for telephone interviews. Our experience has shown that this is not a barrier to participation.

Appendix 2: Informed Consent

#071921

UNIVERSITY OF CALIFORNIA - SAN DIEGO
CONSENT TO ACT AS SUBJECT (CONTROL)

NAME: _____ **DATE:** _____

Igor Grant, MD., and his associates are doing a research study to find out more about how changes in peoples' lives (life stress) influence health and heart disease and blood pressure in a group of spouses of patients with Alzheimer's disease, in comparison to non-caregivers.

You have been asked to take part because you are married and not a caregiver.

If you agree to be in this study, the following will happen to you:

1. You will be interviewed by Dr. Grant or his associates for about two hours either in your home or at another convenient site. This interview will be repeated yearly for five years. You will be asked about the sorts of worries that concern you, changes that have occurred in your life in the recent past, your general state of health, the kinds of people you rely on to help you, and the ways in which you deal with any difficulties that might come up in your life.

2. To check the activity of your stress hormones, Dr. Grant or his associates will take approximately 4 1/2 oz. (8-9 Tbs.) of blood from a vein in your arm. Because the blood factors that are being measured can change as a response to the stress of speaking about problems, the researchers will need several blood samples over the span of about 45 minutes. Blood samples may require two "needle sticks," however to reduce discomfort and to avoid repeated "needle sticks," they may insert a very small needle attached to a tube into one of your forearm veins and leave it in place while you are being interviewed. In this way, they can collect several blood samples from the same place; this blood draw will be repeated each year when you are interviewed. In addition to examination of your stress hormones, we will run several tests on the blood samples that are familiar to you such as measurement of cholesterol, triglycerides, and glucose. We will also run analyses that are less familiar to you including measurement of the sticky molecules in your blood that lead to build-up of plaques in your arteries and measurement of c-reactive protein (a potential indicator of cardiovascular risk) among others. **You will also be asked to submit a urine sample the morning of the blood draw.**

3. In order to determine how responsive you are to stress, you will be asked to speak for about three minutes into a tape recorder about a possible problem such as dealing with a disreputable automobile salesperson. During this time your blood pressure will be taken and samples of blood will be drawn.

4. You have the option of having the results of your blood tests and/or blood pressure sent to your physician. Please indicate whether or not you wish this information to be sent to your physician by checking the appropriate box below:

☐ YES, you wish your test results to be sent to your physician.

☐ NO, you do not want your test results sent to your physician.

5. In order to examine how well you sleep you will be asked to do two things. First you will have one night of your sleep recorded all-night in your own home. Small recording sensors will be taped to your skin on your head, face, torso, and legs. These sensors will record biological signals throughout the night. Laboratory personnel will bring the equipment to you in the evening, and pick it up the following morning. Second, in order to gather longer records of your sleep, you will also be asked to wear a device on your wrist that is about the size of a wrist-watch for the 3-days after your blood draw. This device monitors how much light you are exposed to and how active you are.

6. You will be asked to have a non-invasive ultrasonic image of your carotid arteries (the main artery in your neck) done in your home. You will be asked to lie on your back with your head at the end of the ultrasound scanner. EKG electrodes will be placed in the proper locations for a standard 3-lead EKG. A plastic ring will then be put in place secured under the shoulders to let the sonographer know at what angle the probe is placed at. The sonographer will image both the internal and external carotid arteries using color Doppler. The waveforms generated on Doppler will be compared with representative samples of those for the external and internal carotid artery.

7. You will have a blood pressure cuff placed on one arm, and two small blood pressure cuffs connected to blood pressure measuring devices on the wrist and finger of the other arm in you home. The blood pressure cuff on your arm will be inflated very tightly for 5 minutes. If the tightness of the blood pressure cuff becomes too painful, you may ask that the test be immediately stopped. After the blood pressure cuff is deflated, blood flow in an artery in your arm and the size of the artery will be measured by ultrasound, a harmless, non-invasive method using sound. An ultrasound probe (a small device) will be placed on your arm to measure blood flow and the artery size.

8. After a blood pressure screen (your blood pressure must be 100/60), you will be administered a small tablet of nitroglycerine, a medicine that widens blood vessels under your tongue. Once again, your artery in your arm and the size of the artery will be measured by ultrasound. Nitroglycerin can lower your blood pressure which can make you lightheaded or dizzy. If this should happen to you, you will be asked to remain lying down until the dizziness goes away.

9. In addition to the interview, sleep recordings, and blood draw described above, you will be contacted by telephone once each year to find out how your caregiving situation may have changed. This interview will take about 15 minutes. Because the researchers are interested in how changes in your life may impact your health and the blood indicators they are studying, if you have placed your spouse in a board and care facility, or if they have died, you may be asked to repeat the more intensive interview and blood draw procedures described above. You do not have to answer any questions that you do not wish to. You may ask that the taping be stopped at any time or erased. Only Dr. Grant and his associates will have access to the tapes.

10. Investigators may also wish to use some of your blood for DNA (the genetic material inside your cells) analysis.

a. In addition to Dr. Grant, the specimens collected from you and the DNA that they contain, may also be used in additional research to be conducted by the University of California personnel collaborating in this research, including the following collaborators of Dr. Grant: Drs. Dimsdale, Ziegler, Mills, Patterson, and Ancoli-Israel.
b. It is also possible that in the future a company performing pharmaceutical research would study your DNA in order to learn more about the genetics of high blood pressure and other cardiovascular diseases. Dr. Grant will be responsible for deciding how it will be used.
c. Dr. Grant, his associates, or his successors in these studies will keep your DNA specimen and/or the information derived from it for up to 50 years.
d. This DNA and its derivatives may have significant therapeutic or commercial value. You consent to such uses.

11. Investigators are interested in evaluating your level of physical activity. You will be provided with an accelerometer, which is a small device that records total number of steps you take, time exercising (in minutes), and level (intensity) of exercise. We would like you to wear the accelerometer at your waist during waking hours for three days. You do not need to interact with or use the device during this time; you just need to wear it.

12. Investigators are also interested in your body composition. That is, we would like to assess your height, weight, and bodily circumference of (the distance around) your neck, chest, waist, hip, thigh, and calf. For this, you will be standing up during the measurements and will need to raise the calf of one leg onto a chair or other item to obtain the calf measurement. We would also like to obtain your overall level of body fat. The test involves having you lie comfortably in bed, and then placing two small electrodes to the back of your right hand and two to the top of the right foot. A weak electrical current (less than in a 9 volt battery) is sent between electrodes. The current is imperceptible. From this, fat and lean mass are determined.

Participation in this study may involve some added risks or discomforts. This blood draw might cause pain, bruising, swelling, and extremely rarely, infection, fainting or dizziness. You might experience some skin irritation from the sleep sensors being taped to your skin overnight. When measuring your endothelial activity, the increased pressure in the arm cuff may cause some discomfort and the battery originated charge to the skin may cause some tingling. The interviews and speaking tasks might be emotionally stressful, and will each take from one to two hours of your time. In addition, the presence of a research nurse/technician conducting in-home evaluations and providing training on the sleep monitoring equipment may increase your level of stress. Inflating a blood pressure cuff on your arm for 5 minutes may cause numbness, tingling, or pain in your hand and arm that could last for a few minutes after the blood pressure cuff is released. Nitroglycerine can affect your blood pressure and may cause unusual heartbeats or make you dizzy. Your heart activity will be monitored while these drugs are used.

Should this information about you become known outside the research setting, it may affect your employability and insurability. Please be aware that your confidentiality will be rigorously guarded by assignment of coded numbers to the information that you provide.

Finally, these procedures may involve risks that are currently unforeseeable. You will be, however, informed of any significant research findings relevant to your continued participation.

#071921

If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call The Human Research Protection Program at (858) 455-5050 for more information this, to inquire about your rights as a research subject, or to report research-related problems.

There are no personal benefits to your participation other than the knowledge that participation in this study might help investigators understand better the link between stress and illness. You will not be provided with any results or information regarding your DNA test, however, the investigators may learn more about the genetics of health, high blood pressure, and heart disease. You may learn something about your sleep patterns, your endothial activity, or your blood work, such as your cholesterol levels

Instances are known in which a subject in research has been required to furnish genetic information as a precondition for in applying for health insurance and/or a job. Participation in this study does not mean that you have had genetic testing. Genetic testing means having a test performed and the results provided to you and your doctor. If you are interested in having genetic testing performed you should consult your doctor, as some commercial tests are available. Your doctor can provide you with the necessary information to determine if such a test would be appropriate for you.

If you decide later that you do not want DNA specimens collected from you to be used for future research, you may tell this to Dr. Grant who will use his best efforts to stop any additional studies. However, in some cases, such as if your cells are grown up and are found to be generally useful, it may be impossible to locate and stop such future research once the materials have been widely shared with other researchers.

There are no costs to you for this study. You will receive $100 per year for your participation.

Dr. Grant and/or _____ has explained this study to you and will answer any questions you may have at any time concerning the details of the procedures performed as part of this study. Dr. Grant or his associates may be reached at (858) 534-3652 or (858) 534-3354.

Participation in research is entirely voluntary. You may refuse to participate or withdraw from the study at any time without jeopardy to the medical care you will receive at this institution. Dr. Grant may also discontinue your participation should he believe it is in your best interest. These circumstances may include: collapsed veins preventing blood draw, dizziness or fainting, or a change in your medication that includes one of more exclusionary medications, among other reasons that may be currently unforeseeable.

Research records will be kept confidential to the extent provided by law. Tape recordings will be stored under lock and key for six months and then will be destroyed.

You have received a copy of this consent document and a copy of "The Experimental Subject's Bill of Rights" to keep.

You agree to participate.

---------- ---------- ----------

Subject's Signature Witness Signature Date

_____

Appendix 3: Sociodemographics, Medical Data, & Health History Questionnaires

Caregiver Demographics Form

1. First Name: _____ 2. Middle Initial: ____ 3. Familiar Name: _____

4. Last Name: _____

5. Street Address: _____ 6. Apt/Suite: _____

7. City: _____ 8. State: _____ 9. Zip: _____

10. Home Phone: (_____) _____ - _____ 11. Work Phone: (_____) _____ - _____

12. Long-term Contact Name: _____

13. Street Address: _____ 14. Apt/Suite: _____

15. City: _____ 16. State: _____ 17. Zip: _____

18. Home Phone: (_____) _____ - _____ 19. Work Phone: (_____) _____ - _____

20. Relationship to Caregiver: _____

21. Birth Date: ☐☐ ☐☐ ☐☐☐☐

22. Gender:
- Male....0
- Female....1

23. Ethnicity:
- Not Hispanic or Latino....0
- Cuban....1
- Mexican....2
- Puerto Rican....3
- South or Central American....4
- Other Spanish culture or origin....5

24. Race:
- Black or African American....1
- American Indian or Alaskan Native....2
- Asian....3
- Native Hawaiian or Pacific Islander....4
- White....5

25. Years of Education: ☐☐

26. Type of Diploma: _____

27. Number of Children: ☐☐

28. Marital Status:
- Never Married.....SKIP QUESTION 30.... 0
- Married.... 1
- Divorced.... 2
- Separated.... 3
- Widowed.... 4

29. Number of Years Married: ☐☐

30. Employment Status:
- Never Employed.....SKIP TO QUESTION 35.... 0
- Retired.... 1
- Currently Employed .....SKIP TO QUESTION 33... 2
- Some Employment .....SKIP TO QUESTION 33.... 3

31. Years Retired: ☐☐

32. Average Number of Hours per Week: ☐☐

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

33. Highest Occupation: _____

34. Household Income: | | | | | | mth

35. Relationship to Patient:
- Spouse 1
- Partner 2
- Sibling 3
- Child 4
- Relative 5
- Other - _____ 6

ALZCARE – Alzheimer's Caregiver Research Project dp_demographics

Participant ID: Exam Date: Staff ID: Data Enry Date:

Patient Demographics

1. First Name: _____ 2. Middle Initial: ____ 3. Familiar Name: _____
4. Last Name: _____

5. Caregiver Study ID: ☐☐☐☐☐

6. Birth Date: ☐☐ ☐☐ ☐☐☐☐

7. Year Alzheimer's Diagnosed: ☐☐☐☐

8. Gender:
   - Male....0
   - Female....1

9. Ethnicity:
   - Not Hispanic or Latino....0
   - Cuban....1
   - Mexican....2
   - Puerto Rican....3
   - South or Central American....4
   - Other Spanish culture or origin....5

10. Race:
    - Black or African American....1
    - American Indian or Alaskan Native....2
    - Asian....3
    - Native Hawaiian or Pacific Islander....4
    - White....5

11. Years of Education: ☐☐

12. Type of Diploma: _____

13. Number of Children: ☐☐

14. Marital Status:
    - Never Married.....SKIP QUESTION 16.... 0
    - Married.... 1
    - Divorced.... 2
    - Separated.... 3
    - Widowed.... 4

15. Number of Years Married: ☐☐

16. Employment Status:
    - Never Employed.....STOP.... 0
    - Retired.... 1
    - Currently Employed .....SKIP TO QUESTION 19... 2
    - Some Employment .....SKIP TO QUESTION 19.... 3

17. Years Retired: ☐☐

18. Average Number of Hours per Week: ☐☐

19. Highest Occupation: _____

Caregiver Health and Health Behaviors

Participant ID# _____

The next set of questions is in regard to your health.

	RC13	Excellent	Very Good	Good	Fair	Poor
1.	In general, would you say your health is:	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

	RC14	Much better now	Somewhat better now	About the same	Somewhat worse now	Much worse now
2.	Compared to 2 months ago, how would you rate your health in general now?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

	Do you currently have, or has a doctor told you that you have, any of the following health problems?	No	Yes
3.	Arthritis	0 ☐	1 ☐
4.	Hypertension (i.e., High Blood Pressure)	0 ☐	1 ☐
5.	Heart Attack (Myocardial Infarction)	0 ☐	1 ☐
6.	Congestive Heart Failure	0 ☐	1 ☐
7.	Angina (Chest pain due to your heart)	0 ☐	1 ☐
8.	Heart Disease (other than heart attack, congestive heart failure, or angina). Specify _____	0 ☐	1 ☐
9.	Chronic Lung Disease not including asthma (e.g., Chronic Bronchitis or Emphysema)	0 ☐	1 ☐
10.	Diabetes (not including "pre-diabetes")	0 ☐	1 ☐
11.	Stroke or Transient Ischemic Attack (TIA)	0 ☐	1 ☐
12.	Stomach ulcers, irritable bowel syndrome, inflammatory bowel disease, or any other serious problems with your stomach or bowels	0 ☐	1 ☐
13.	Problems with your kidneys	0 ☐	1 ☐
14.	Cirrhosis or any other serious liver problem (i.e., Hepatitis)	0 ☐	1 ☐
15.	Cancer If yes, what kind _____	0 ☐	1 ☐

Participant ID# ____

	Do you currently have, or has a doctor told you that you have, any of the following health problems?	No	Yes
16.	Problems with your vision or hearing	0 ☐	1 ☐
17.	High cholesterol	0 ☐	1 ☐
18.	In the past, have you ever been diagnosed with, or received treatment for, emotional or psychiatric problems? If yes, what? _____	0 ☐	1 ☐
19.	Any other health problems that I have not asked you about? If yes, what? _____	0 ☐	1 ☐

	In the past month, have you experienced the following symptoms?	No	Yes	How many days did you have the symptom(s)?
20.	Temperature of 100 degrees F (37.7 C) or more	0 ☐	1 ☐	__ __
21.	Headache lasting more than 1 hour	0 ☐	1 ☐	__ __
22.	Skin rash or hive	0 ☐	1 ☐	__ __
23.	Painful, irritated, or burning eyes	0 ☐	1 ☐	__ __
24.	Ear ache or ear infection	0 ☐	1 ☐	__ __
25.	Toothache	0 ☐	1 ☐	__ __
26.	Sore throat	0 ☐	1 ☐	__ __
27.	Sneezing, stuffy, or runny nose	0 ☐	1 ☐	__ __
28.	Dry cough (more than occasional)	0 ☐	1 ☐	__ __
29.	Coughing up substances other than saliva, or thin phlegm	0 ☐	1 ☐	__ __
30.	Wheezing (from chest)	0 ☐	1 ☐	__ __
31.	Unusual shortness of breath	0 ☐	1 ☐	__ __
32.	Unplanned weight loss	0 ☐	1 ☐	__ __

Participant ID#

In the past month, have you experienced the following symptoms?	No	Yes	How many days did you have the symptom(s)?
33. Nausea and/or vomiting	0 ☐	1 ☐	__ __
34. Stomach pain or abdominal cramps	0 ☐	1 ☐	__ __
35. Heartburn	0 ☐	1 ☐	__ __
36. Chest pain other than heartburn	0 ☐	1 ☐	__ __
37. Unanticipated Rapid or pounding heart (not associated with exercise)	0 ☐	1 ☐	__ __
38. Diarrhea	0 ☐	1 ☐	__ __
39. Bloody or black stools	0 ☐	1 ☐	__ __
40. Discomfort with hemorrhoids	0 ☐	1 ☐	__ __

RC15	0 days	1 or 2 days	3 to 5 days	6 to 9 days	10 to 19 days	20 to 29 days	All 30 days
41. During the past 30 days, on how many days did you have at least one drink containing alcohol (not include a few sips of wine for religious purposes)?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

RC16	None	< 1 drink	1 drink	2 drinks	3 drinks	4 drinks	5 or more drinks
42. During the past 30 days, on the days you drank alcohol, how many drinks did you usually drink?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

RC15	0 days	1 or 2 days	3 to 5 days	6 to 9 days	10 to 19 days	20 to 29 days	All 30 days
43. During the past 30 days, on how many days did you smoke cigarettes?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

Participant ID# ____

44. One the typical day, how many cigarettes do you smoke? _____

RC15

	0 days	1 or 2 days	3 to 5 days	6 to 9 days	10 to 19 days	20 to 29 days	All 30 days
45. During the past 30 days, on how many days did you use any other forms of tobacco, such as smoking a pipe or chewing tobacco?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐

	No	Yes
46. Have you previously been a smoker and quit permanently?	0 ☐	1 ☐

47. How many years did you smoke? (Enter '0' if never smoked). __ __

48. How tall are you? __ feet, __ __ inches (total, in inches) __ __

49. How much do you weigh? __ __ __ lbs

Rapid Assessment of Physical Activity

Physical Activities are activities where you move and increase your heart rate above its resting rate, whether you do them for pleasure, work, or transportation.

The following questions ask about the amount and intensity of physical activity you usually do. The intensity of the activity is related to the amount of energy you use to do these activities.

Examples of physical activity intensity levels:

Light activities • your heart beats slightly faster than normal • you can talk and sing	 Walking Leisurely  Stretching  Vacuuming or Light Yard Work
Moderate activities • your heart beats faster than normal • you can talk but not sing	 Fast Walking  Aerobics Class  Strength Training  Swimming Gently
Vigorous activities • your heart rate increases a lot • you can't talk or your talking is broken up by large breaths	 Stair Machine  Jogging or Running  Tennis, Racquetball, Pickleball or Badminton

Participant ID# _____

RC17	0 days	1 or 2 days	3 or 4 days	5 or 6 days	Every Day
In a typical week, how often do you do light exercises?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

RC17	0 days	1 or 2 days	3 or 4 days	5 or 6 days	Every Day
In a typical week, how often do you do moderate exercises?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

RC18	< 10 minutes	10-19 minutes	20-29 minutes	30 minutes or more
On days that you do moderate activities, how much time do you spend doing them?	0 ☐	1 ☐	2 ☐	3 ☐

RC17	0 days	1 or 2 days	3 or 4 days	5 or 6 days	Every Day
In a typical week, how often do you do vigorous exercises?	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐

RC18	< 10 minutes	10-19 minutes	20-29 minutes	30 minutes or more
On days that you do vigorous activities, how much time do you spend doing them?	0 ☐	1 ☐	2 ☐	3 ☐

	No	Yes
Do you engage in activities to increase muscular strength, such as lifting weights or calisthenics, once a week or more?	0 ☐	1 ☐
Do you engage in activities to improve flexibility, such as stretching or yoga, once a week or more	0 ☐	1 ☐

Participant ID# _____

		False	True
0.	Participant rarely or never does any physical activities.	0 ☐	1 ☐
1.	Participant does some light or moderate physical activities, but not every week.	0 ☐	1 ☐
2.	Participant does some light physical activity every week.	0 ☐	1 ☐
3.	Participant does moderate physical activities less than 30 minutes a day or fewer than 5 days a week.	0 ☐	1 ☐
4.	Participant does vigorous physical activities less than 20 minutes a day or fewer than 3 days a week.	0 ☐	1 ☐
5.	Participant does 30 minutes or more a day of moderate physical activities, 5 or more days a week.	0 ☐	1 ☐
6.	Participant does 20 minutes or more a day of vigorous physical activities, 3 or more days a week.	0 ☐	1 ☐
1.	Participant does activities to increase muscular strength, such as lifting weights or calisthenics, once a week or more.	0 ☐	1 ☐
2.	Participant does activities to improve flexibility, such as stretching or yoga, once a week or more.	0 ☐	1 ☐

Appendix 4: Psychological Questionnaires

Center for Epidemiologic Studies – Depression Scale 10

Participant ID# _____

These questions deal with statements people might make about how they feel. For each of the statements, please indicate how often you felt that way during **the past week**.

	RC20	Rarely or none of the time (< 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or almost all the time (5-7 days)
1.	You were bothered by things that don't usually bother you.	0 ☐	1 ☐	2 ☐	3 ☐
2.	You had trouble keeping your mind on what you were doing.	0 ☐	1 ☐	2 ☐	3 ☐
3.	You felt depressed.	0 ☐	1 ☐	2 ☐	3 ☐
4.	You felt that everything you did was an effort.	0 ☐	1 ☐	2 ☐	3 ☐
5.	You felt hopeful about the future.	0 ☐	1 ☐	2 ☐	3 ☐
6.	You felt fearful.	0 ☐	1 ☐	2 ☐	3 ☐
7.	Your sleep was restless.	0 ☐	1 ☐	2 ☐	3 ☐
8.	You were happy.	0 ☐	1 ☐	2 ☐	3 ☐
9.	You felt lonely.	0 ☐	1 ☐	2 ☐	3 ☐
10.	You could not get going.	0 ☐	1 ☐	2 ☐	3 ☐

Role Overload

Participant ID# _ _ _ _

DIRECTIONS: These next questions relate to your energy level and the time it takes to do the things you have to do. How much does each statement describe you? **RC1**

		Not at all	Somewhat	Quite a bit	Completely
1.	You are exhausted when you go to bed at night.	0 ☐	1 ☐	2 ☐	3 ☐
2.	You have more things to do than you can handle.	0 ☐	1 ☐	2 ☐	3 ☐
3.	You don't have time just for yourself.	0 ☐	1 ☐	2 ☐	3 ☐
4.	You work hard but never seem to make any progress.	0 ☐	1 ☐	2 ☐	3 ☐