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Sleep and cardiovascular disease in Alzheimer's caregivers: An examination of cross-sectional and longitudinal associations and potential treatment response

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in

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by

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
BA	Behavioral Activation
BIF	Bifurcation
BMI	Body Mass Index
BRS	Baroreflex Sensitivity
CAC	Coronary Artery Calcium
CAR	Circadian Activity Rhythms
CCA	Common Carotid Artery
CDR	Caregiver Dementia Rating Form
CES-D	Center for Epidemiological Studies Depression Scale
CG	Caregiver
CHD	Coronary Heart Disease
COMT	Catechol-O-methyltransferase
CRP	C-reactive Protein
CVD	Cardiovascular Disease
DSM 5	Diagnostic and Statistical Manual 5
ELISA	Enzyme-linked Immunosorbent Assay
EPI	Epinephrine
FMD	Flow-mediated Dilation
HPA	Hypothalamic-pituitary-adrenal
HR	Heart Rate
ICSD-3	International Classification of Sleep Disorders 3
IL-6	Interleukin 6
IMT	Intima-media Thickness
INT	Internal Carotid Artery
IS	Information Support
ISI	Insomnia Severity Index
MAP	Mean Arterial Pressure
MMPI-2	Minnesota Multiphasic Personality Inventory
NA	Negative Affect
NE	Norepinephrine
PA	Positive Affect
PAI-1	Plasminogen Activator Inhibitor 1
PHQ-2	Patient Health Questionnaire 2
PSG	Polysomnogram
PSQI	Pittsburgh Sleep Quality Index
RAPA	Rapid Assessment of Physical Activity
RCPR	Response-contingent Positive Reinforcement
RMBC	Revised Memory and Behavior Checklist
SAM	Sympathomedullary
TST	Total Sleep Time
TNF-α	Tumor Necrosis Factor Alpha
vWF	von Willebrand Factor Antigen
ZBI	Zarit Burden Inventory

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PUBLICATIONS

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ABSTRACT OF THE DISSERTATION

Sleep and cardiovascular disease: An examination of cross-sectional and longitudinal associations and potential treatment response

by

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Doctor of Philosophy in Clinical Psychology

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Rationale: Alzheimer's caregivers are at increased risk for cardiovascular disease (CVD) and exhibit higher levels of vascular dysfunction compared to non-caregivers. Sleep has been implicated in the pathogenesis of CVD, however this relationship is not fully understood. Behavioral Activation therapy has shown promise for reducing caregiver distress and decreasing circulating levels of IL-6, and improvements in sleep may mediate these effects. The purpose of the current study is to examine the cross-sectional and longitudinal associations of subjective and

objective measures of sleep with markers of CVD risk in Alzheimer's caregivers and test the efficacy of a brief Behavioral Activation intervention for improving sleep.

Design: This dissertation used archival data from two studies. Study 1 was a longitudinal study in which 126 spousal caregivers and 60 non-caregiver controls were assessed annually over 5 years. Study 2 was a randomized controlled trial of Alzheimer's caregivers testing the efficacy of a brief Behavioral Activation intervention (n = 75) versus an Information Support condition (n = 76) to reduce caregiver distress and markers of CVD risk. Subjective sleep quality and quantity were assessed using the Pittsburgh Sleep Quality Index and Insomnia Severity Index. Objective sleep data including circadian rhythm profiles were obtained from actigraphy records using Actiwatch. Data for markers of CVD risk were obtained through several methods including ultrasounds of the brachial and carotid arteries, blood pressure and baroreflex sensitivity, and blood and urine samples for catecholamine levels and markers of endothelial function. Using a combined sample, bivariate associations and multiple linear regression models were fitted to test associations between sleep variables and markers of CVD risk. Using data from Study 1, longitudinal associations were tested using multilevel models to examine associations between sleep measures and markers of CVD risk over time. Using data from Study 2, multilevel models and ANOVAs were used to test the impact of a brief Behavioral Activation intervention on various measures of sleep.

Results: Regression analyses of baseline associations showed several significant associations between circadian activity rhythms and CVD risk markers. Caregivers with less robust circadian rhythms exhibited impaired baroreflex sensitivity and increased levels of tumor necrosis factor alpha, von Willebrand factor antigen, and plasminogen activator inhibitor 1. Longitudinal analyses revealed that after controlling for caregiver physical activity, stress, and

sex; percent sleep was significantly associated with resting heart rate and norepinephrine. Caregivers with higher percent sleep experienced lower resting heart rate at baseline but showed a slower decrease over time. Caregivers with higher percent sleep also exhibited higher levels of norepinephrine at baseline; there was no significant effect on norepinephrine levels over time. There was not a significant effect of the intervention on sleep outcomes.

Conclusions: Cross-sectionally, caregivers with less robust circadian activity rhythm profiles exhibit markers suggestive of increased CVD risk. However, this study revealed little evidence of longitudinal associations between measures of sleep and markers of CVD risk over time. Furthermore, the Behavioral Activation intervention was not more effective than the control condition at improving caregivers' sleep.

Chapter 1: Background and Significance

1.1 Cardiovascular disease

Cardiovascular disease (CVD) is a highly prevalent medical issue that remains the leading cause of death both in the United States and globally (Benjamin, Muntner, & Bittencourt, 2019; Global Health Estimates 2016). In the United States, it is estimated that the prevalence of CVD (comprising coronary heart disease, heart failure, stroke, and hypertension) in adults ≥20 years of age is 48.0% overall (121.5 million in 2016) and increases with age in both males and females. CVD prevalence excluding hypertension is 9.0% overall (24.3 million in 2016). The healthcare costs associated with CVD are exorbitant. The estimated direct and indirect costs for CVD from 2014 to 2015 was $351.2 billion, and this number is projected to surpass $1 trillion by 2035 (Khavjou, Phelps, & Lieb, 2016). Furthermore, CVD currently claims approximately 840,000 lives annually; more lives than cancer and chronic lung disease combined (Benjamin et al., 2019).

1.2 CVD Risk Factors and Prevention

Among the many identified risk factors for CVD; high blood pressure, high cholesterol, and smoking are three key contributors to the future development of CVD (Roth et al., 2018). A recent study using the Global Burden of Disease methodology found that a large proportion of CVD is attributable to (in order of decreasing contribution) dietary risk, high systolic blood pressure, high BMI, high total cholesterol level, high fasting plasma glucose level, tobacco smoking, and low levels of physical activity (Friar, Chen, & Li, 2012). The age-adjusted death rate attributable to CVD has decreased over the past 15 years (Benjamin et al., 2019) due not only to increased use of evidence-based medical therapies for secondary prevention, but also to changes in risk factors in the population attributable to lifestyle and environmental changes

(CDC, 2005). The identification of additional risk factors and mechanisms in the development of CVD could further improve our ability to prevent this deadly disease.

1.3 Sleep and CVD

Several aspects of sleep including quantity of sleep (sleep duration), quality of sleep, or the presence of a sleep disorder (e.g., sleep apnea) have been associated with CVD and stroke. It has now been known for almost 20 years that complaints of insomnia, independent of sleep apnea, are associated with increased rates of CVD (Schwartz, 1999). Due to wide variations in how insomnia has been defined and measured in the research literature, there are conflicting data regarding the association of insomnia and CVD and caution must be exercised when comparing studies and interpreting results (Javaheri & Redline, 2017). Nonetheless, a recent meta-analysis estimated that insomnia was associated with a 45% increased risk of developing or dying from CVD (*RR* = 1.45, *95% CI:* 1.29–1.62; $p < 0.01$; Sofi et al., 2014), and research suggests that this risk is greater when insomnia is accompanied by short sleep duration.

1.4 Purported Mechanisms

Although the pathogenesis of insomnia and CVD is not fully understood, there are several possible mechanisms that could explain the relationship. Javaheri and Redline (2017) outline multiple potential mechanisms, including dysregulation of the hypothalamic-pituitary adrenal (HPA) axis, abnormal modulation of the autonomic nervous system, increased sympathetic nervous system activity, increased systemic inflammation, and increased atherogenesis. Chronic activation or dysregulation of the HPA axis may lead not only to increased risk of CVD but also to insulin resistance, diabetes, and mental health disorders such as anxiety and depression. To that end, insomnia/short sleep duration are associated with

impaired glucose metabolism and diabetes, which may serve as mediators on the pathway to CVD.

It should be noted that insomnia and short sleep duration affect distinct albeit overlapping populations. The current classification of insomnia in the newest editions of both the International Classification of Sleep Disorders (ICSD-3), and the Diagnostic and Statistical Manual of Mental Disorders (DSM 5), have attempted to clarify past nosologies by simplifying the insomnia criteria. Both nosologies now define insomnia based on two primary criteria: A) a predominant complaint of dissatisfaction with sleep quantity or quality, associated with difficulty initiating sleep, maintaining sleep, and/or early morning awakening with inability to return to sleep, and B) the sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. Short sleep duration is not a required criterion for a diagnosis of insomnia but often co-occurs with the disorder. Data from the Sleep Heart Health Study showed that in a prospective analysis of 631 participants with insomnia symptoms, 48% of participants also had a sleep duration of < 6 h assessed by polysomnography (PSG; Bertisch et al., 2018).

1.5 Assessing Sleep Quality and Quantity

Due to the many ways of characterizing sleep, there are several methods of assessing sleep quality, quantity, and diagnostic constructs. Establishing a diagnosis of insomnia is best accomplished through clinical interview. Clinicians obtain a thorough sleep history and generally have patients complete sleep diaries to ascertain the specific deficits in patients' sleep patterns and rule out other potential explanations (e.g., circadian phase disorder, restricted sleep time). Thus, the diagnosis of insomnia depends wholly on synthesizing data from patients' subjective reports. Several well validated self-report measures also exist that assess various components of

sleep in research settings such as the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and the Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001). These measures may be administered in addition to a clinical interview or are often used alone to obtain data on participants' sleep.

Assessing sleep quantity can be achieved either by self-report or through objective measurement; however, these methods may not assess precisely the same constructs. Subjective sleep quantity is typically obtained by asking patients, "How many hours of sleep do you usually get a night (or when you usually sleep)?" Approximately 50 years ago, the invention of polysomnography and standardized assessment methods (Rechtschaffen, 1968) allowed for in-lab objective recordings of sleep; including measures of sleep duration, continuity, timing, and architecture. The later advent of actigraphy allowed for similar objective recordings of sleep duration, continuity, and timing in patients' natural sleep environments (Ancoli-Israel et al., 2003).

Studies comparing subjective reports and objective measures of sleep duration (i.e., actigraphy or polysomnography) reveal significant discrepancies that are systematically biased dependent on various psychosocial and sleep characteristics. Data from the CARDIA Sleep Study suggest that individuals tend to overestimate their sleep duration; participants obtaining 5 hours of sleep overestimated sleep duration by 1.3 hours while those obtaining 7 hours overestimated by 0.3 hours. There was a correlation of only 0.45 between subjective reports and objectively assessed sleep duration (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008). In the Rotterdam Study, 34% of participants showed deviations in subjective and objective sleep duration of greater than 1 hour. Individuals obtaining shorter sleep tended to overestimate their sleep duration, while subjectively poor sleepers tended to underestimate their total sleep time

(Van Den Berg et al., 2008). Fernandez-Mendoza and colleagues (2011) observed that objectively short sleepers tended to overestimate their sleep duration, but individuals with insomnia reported less sleep than controls with similar objective sleep duration. Furthermore, they found different MMPI-2 profiles when comparing insomniacs with normal and short sleep duration; insomniacs with normal sleep duration showed a MMPI-2 profile of high depression and anxiety, and low ego strength, whereas insomniacs with short sleep duration showed a profile suggestive of a medical disorder. These observations have led some researchers to speculate that subjective sleep complaints may reflect an underlying psychological vulnerability while objective sleep deficits are more closely associated with poorer physical health outcomes (Vgontzas, Fernandez-Mendoza, Liao, & Bixler, 2013), however more empirical studies are needed that assess and analyze outcomes related to both constructs.

1.6 Review of the Literature

The use of different measurements of sleep across studies has led to some discrepant results in the literature regarding the association of sleep and CVD. However, the literature overall supports sleep disturbance as a potential risk factor for CVD. Sofi and colleagues (2014) conducted a meta-analysis investigating the longitudinal association of insomnia with incident CVD in cohort studies, finding a 45% increased incidence of CVD in individuals with subjective insomnia complaints. Cappuccio and colleagues (2011) found that subjectively short sleep duration was associated with a greater risk of developing or dying of coronary heart disease (CHD; $RR = 1.48$, 95% CI: [1.22, 1.80], $p < .01$), stroke ($RR = 1.15$, 95% CI: [1.00, 1.31], $p < 0.05$), but not total CVD ($RR = 1.03$, 95% CI: [0.93, 1.15], $p = 0.52$). Yin et al. (2017) investigated the dose-response relationships of subjective sleep duration with risk of all-cause

mortality, total CVD, CHD, and stroke. For total CVD, the pooled *RR* was 1.06 (95% *CI*: [1.03, 1.08], $p < .05$) per 1-hour reduction of sleep duration.

Various characteristics of sleep have been associated with a host of potential mediators of CVD and CVD risk factors. Studies have shown varying levels of evidence supporting associations of subjective and objective sleep quality and duration with coronary artery calcium (CAC), carotid intima-media thickness (IMT), flow-mediated dilation (FMD), and arterial stiffness (Aziz et al., 2017). Several reviews have demonstrated an association between subjective and objective sleep duration and incident diabetes and increased BMI (Knutson, 2011; Cappuccio, D'Elia, Strazzullo, & Miller, 2010; Schultes, Schmid, Peters, Born, & Fehm, 2005). Subjective and objective sleep duration have also been associated with high blood pressure and the development of hypertension (Guo et al., 2013). Subjective sleep quality, and both subjective and objective sleep duration are associated with increased levels of systemic inflammation as reflected by higher levels of Interleukin-6 (IL-6) and C-reactive protein (CRP; Irwin, Olmstead, & Carroll, 2016).

Considering subjective and objective sleep disturbances as separate constructs has led some researchers to investigate their interaction in association with CVD, established risk factors, and potential mediating variables. Bertisch and colleagues (2018) found that individuals with both objectively short sleep duration and insomnia/poor sleep showed significantly elevated risk of experiencing incident CVD over the course of the follow-up period (*HR*: 1.29, 95% *CI*: [1.00, 1.66], $p < .05$). Neither the associations of insomnia/poor sleep only nor objectively short sleep duration only with incident CVD were statistically significant. A review of studies examining the potential interaction of objectively short sleep and insomnia (Bos, 2019) found that objectively short sleep duration either increased the risk of various CVD related processes

compared to the risk associated with insomnia/subjective sleep complaints alone (hypertension: Bathgate, Edinger, Wyatt, & Krystal, 2016; Hien, Lanquart, Loas, Hubain, & Linkowski, 2019; heart rate and heart rate variability: Spiegelhalder et al., 2011; Jarrin et al., 2018; blunted diurnal cortisol profile: Castro-Diehl et al., 2015; IMT: Nakazaki et al., 2012) or found a significant interaction of objectively short sleep duration and CVD related processes (hypertension: Fernandez-Mendoza et al., 2012; Vgontzas, Liao, Bixler, Chrousos, & Vela-Bueno, 2009a; diabetes, Vgontzas et al., 2009b). These findings support the theory that insomnia with objectively short sleep duration may be a particularly severe phenotype of the disease and suggest that more studies should evaluate both subjective and objective sleep disturbance.

1.7 Circadian Rhythms and CVD

In addition to characteristics of sleep like sleep duration and sleep efficiency, circadian rhythms may also be important to cardiovascular health. Many cardiovascular physiological parameters (e.g., heart rate, blood pressure, electrocardiogram indices) and pathophysiological events (e.g., myocardial ischemia/infarction, sudden cardiac death) show circadian rhythms (Guo & Stein, 2003). Blood pressure exhibits a natural dipping at night that occurs with normal sleep. Some researchers speculate that this dipping may be important to cardiovascular health and have termed the effect a "cardiovascular holiday" (Trinder, Waloszek, Woods, & Jordan, 2012). Furthermore, the incidence of myocardial ischemia or infarction or sudden cardiac death appears highest in the morning hours, and this may be due to a surge in blood pressure at the end of the sleep period (Giles, 2006). Consequently, circadian misalignment of sleep may be associated with negative health outcomes related with CVD. Scheer, Hilton, Mantzoros, and Shea (2009) showed that participants subjected to a 12-hour phase shift in sleep time exhibited decreased leptin, increased glucose (despite increased insulin), increased mean arterial compliance, reduced

sleep efficiency, and completely reversed daily cortisol rhythms. These results suggest that the circadian timing of sleep may also be significantly related to CVD outcomes.

1.8 Caregivers, CVD, and Sleep

Caregivers (CG) exhibit increased markers of CVD risk and vascular pathology. CGs caring for a patient with moderate or severe dementia demonstrated significant reductions in FMD compared to non-caregivers and CGs of patients with mild dementia (Mausbach et al., 2010). Duration of caregiving is significantly associated with IMT of the carotid artery, and caregivers are more likely to have carotid plaques compared to non-caregivers (Roepke et al., 2011). CGs also exhibit compromised arterial compliance, reduced baroreflex sensitivity (Lucini et al., 2008), accelerated risk of hypertension (Shaw et al., 1999), and increased biomarkers of inflammation and procoagulant shift (e.g., D-Dimer, TNF-α, IL-6; Mills et al., 2009).

Many of the adverse vascular associations of caregiving and sleep overlap, suggesting that one explanation for the observed increased vascular risk in CGs is sleep disturbance. While age alone is associated with lower sleep efficiency, less slow-wave sleep, and more stage 1 sleep in both CGs and non-caregivers; CGs of patients with moderate to severe Alzheimer's disease reported significantly more sleep problems and more functional impairment because of sleepiness than non-caregivers. Objectively, older caregivers of those with moderate to severe Alzheimer's disease sleep less than older non-caregivers (McKibbin et al., 2005).

Previous research conducted by the UCSD Alzheimer's Caregiver Project has shown some associations between sleep variables and markers of CVD risk. Controlling for relevant CVD risk factors including age, sex, blood pressure, and BMI; increased wake after sleep onset (assessed by PSG) was positively associated with norepinephrine and D-dimer in a sample of 40 CGs (Mausbach et al., 2006). CGs demonstrate both higher levels of D-dimer and lower levels of

total sleep time and sleep efficiency (assessed by PSG) compared to non-caregiving controls. Furthermore, longer wake after sleep time predicts IL-6 controlling for age and BMI (von Känel et al., 2006). Another study used both subjective sleep assessments and 3-night actigraphy to obtain objective sleep parameters and investigate associations with biomarkers of atherosclerosis. There were independent associations between decreased subjective sleep quality and increased levels of D-dimer and von Willebrand factor antigen (vWF) in all participants (i.e., caregivers and non-caregivers) and significantly stronger associations between decreased sleep efficiency and elevated levels of IL-6 and CRP in caregivers compared to controls (von Känel et al., 2010). These findings provide some explanation for the increased CVD risk in elderly poor sleepers, and CGs in particular. However, it should be noted that logistic regression models examining cross-sectional associations between objective sleep duration and efficiency with odds of having diabetes, dyslipidemia, or hypertension found no significant relationship (Schwartz et al., 2013). It is possible that more time is needed to observe an association between sleep variables and vascular pathology (e.g., longitudinal studies). Furthermore, several of these associations demonstrated clinically relevant magnitudes, but more power may be necessary to achieve significance.

1.9 Behavioral Activation for Caregivers

Behavioral Activation (BA) therapy may be effective for reducing CG distress and associated markers of CVD risk and improve CG sleep quantity and quality. The theory of BA is based on Lewinsohn's model of depression (1974) which posits that depression is a consequence of low levels of response-contingent positive reinforcement (RCPR). In other words, depression occurs when individuals experience low levels of pleasurable activities and high levels of activity restriction (Williamson & Shaffer, 2000). Past research has demonstrated that depressive

symptoms are more prevalent in CGs relative to non-caregivers and have revealed associations between depressive symptoms and the diagnosis of CVD in this population. In a meta-analysis of several caregiving populations (e.g., dementia, cancer, stroke), there is a mean correlation of 0.34 between activity restriction and depression (Mausbach et al., 2011). This correlation reaches as high as 0.65 in dementia CGs (Mausbach, Patterson, & Grant, 2008). Of particular relevance, CGs with high levels of pleasurable activities and low levels of activity restriction (HPLR) have significantly lower blood pressure relative to those with low levels of pleasurable activities and high levels of activity restriction (LPHR; Chattillion et al., 2012). Individuals with HPLR also exhibited significantly better subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbance, and daytime dysfunction compared to CGs with LPHR (Moore et al., 2011).

BA therapy is an evidence-based behavioral treatment for depression that seeks to reduce activity restriction and restore engagement in pleasurable and rewarding activities. A brief BA intervention (6 weeks) was designed to reduce CVD risk and depressive symptoms in CGs. In a randomized trial comparing this intervention to a time-equivalent Information-Support (IS) condition, participants receiving BA had significantly greater reductions of IL-6, depressive symptoms, and negative affect from pre- to post-treatment (Moore et al., 2013). The efficacy of BA to improve subjective and objective sleep parameters has not been investigated. However, longitudinal studies have shown that positive affect (PA) is associated with better subjective sleep over time (von Känel et al., 2014), suggesting increasing levels of RCPR could result in improved sleep.

1.10 Summary and Limitations of Prior Research

Research has shown that sleep and caregiving are each independently associated with CVD risk either via processes underlying CVD or as evidenced by vascular pathology. However,

there is a need for studies to dissect the differential contributions of subjective and objective sleep parameters in these associations. Furthermore, the potential risk associated with the circadian timing of sleep has yet to be thoroughly explored. Greater understanding of the negative health impacts of sleep disturbance in the elderly and CGs in particular could reveal new intervention targets and inform the development of new behavioral treatments to reduce CVD risk in this population.

1.11 Specific Aims

The purpose of this dissertation was to examine the associations of various sleep variables with multiple markers of CVD risk and vascular pathology in Alzheimer's caregivers and investigate the potential utility of a brief Behavioral Activation intervention to improve sleep quality and quantity. Specifically, the study examined processes thought to be mechanistically related to the development of CVD or that reflect current vascular pathology. These outcomes included markers of systemic inflammation, markers of blood coagulation, blood pressure, SAM arousal, flow-mediated dilation, intima-media thickness of the carotid artery, and baroreflex sensitivity. Greater understanding of the specific risks and potential treatment of sleep disturbance could lead to greater awareness of the association between sleep and CVD, greater knowledge of potential mechanisms driving this association, and consequently, more thorough sleep assessment in populations at risk for CVD, and improved CVD prevention measures. This study featured several unique characteristics. It is one of the first studies to examine the associations of sleep and CVD in Alzheimer's caregivers, providing insights into this CVD risk factor in an at-risk population. Also, this study utilized multiple assessments of sleep quality and quantity, including subjective reports from valid and reliable self-report measures, objective sleep data from wrist actigraphy as well as derived measures of circadian activity rhythms. The

inclusion of these related but distinct constructs allowed for the examination of differential associations with specific markers of CVD risk.

Specific aims and hypotheses were:

Aim 1: Examine cross-sectional associations between subjective and objective sleep measures, circadian activity rhythm (CAR) and markers of CVD risk in Alzheimer's caregivers. This aim expanded on previous research showing cross-sectional associations of subjective sleep impairment and increased coagulation and endothelial dysfunction, and objective sleep impairment and increased inflammatory biomarkers. Hypothesis 1: Various measures of sleep quality (i.e., PSQI and ISI scores) and quantity (i.e., Actigraphy total sleep time, percent sleep, and circadian activity rhythm variables) will be negatively associated with markers of CVD risk; impaired sleep will be associated with greater vascular pathology.

Aim 2: Observe longitudinal associations between subjective and objective sleep measures, CAR, and markers of CVD risk in Alzheimer's caregivers. This aim explored potential associations between subjective and objective measures of sleep and markers of CVD risk over time. Hypothesis 2: Sleep measures and vascular pathology will be interrelated such that impaired sleep will predict increased markers of CVD risk over time.

Aim 3: Test the ability of a brief BA intervention to improve subjective and objective sleep measures and CAR variables in Alzheimer's caregivers. If sleep disturbance is related to higher risk for markers of CVD risk and vascular pathology in CGs, then it is important to determine if interventions can improve sleep quality and potentially reduce CVD risk. Hypothesis 3: CGs in the BA group will show greater improvements in sleep measures compared to CGs in the Information Support (IS) group.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Brent Mausbach, Ph.D., Sonia Ancoli-Israel, Ph.D., Igor Grant, M.D., Jonathan Helm, Ph.D., and Vanessa Malcarne, Ph.D. The dissertation author was the primary investigator and author of this material.

Chapter 2: Methods

2.1 Overview of Studies

The proposed dissertation used archival data from two studies assessing the association of caregiving and various markers of CVD risk and vascular pathology. The theoretical model guiding these research studies was based on the concept of psychobiological vulnerability. Specifically, CG distress (e.g., depressive symptoms, sleep disturbance) was posited as a key mediator of physiological processes that have been linked to CVD and stroke.

Study 1

This longitudinal study of 126 spousal Alzheimer's CGs and 60 non-caregiver controls assessed participants annually for up to 5 years to examine associations between caregiver stress, markers of CVD risk, and vascular pathology. Each annual assessment consisted of a psychosocial assessment battery, medical assessments, and collection of objective sleep data via actigraphy (3-day timeframe). Due to the rolling recruitment strategy of the study, participants recruited later than the first year had less possible assessments (e.g., participants recruited in year 2 had a maximum of four possible assessments). Additionally, many participants experienced a change in CG status during the study (i.e., care recipient was placed in care facility or passed). Although these participants continued to be assessed, the change in CG status introduced a variable that was difficult to control. These cases were censored in analyses. Therefore, all 126 CGs have a baseline assessment, 93 were assessed at 1-year follow-up, 64 at 2-year follow-up, 42 at 3-year follow-up, and 7 at 4-year follow-up (i.e., year 5). Similar decreases are observed in non-caregivers assessed over time. All 60 non-caregivers were assessed at baseline, 55 were assessed at 1-year follow-up, 49 at 2-year, 40 at 3-year, and 12 at 4-year.

Study 2

This intervention study of Alzheimer's caregivers (n=172) tested the efficacy of a brief Behavioral Activation intervention (n=75) compared to an Information Support condition (n=76) to reduce caregiver distress and markers of CVD risk (21 participants were not randomized but have baseline data). Participants were assessed at baseline, post-treatment, 6-, and 12-months post-therapy. Like Study 1, each assessment consisted of a psychosocial assessment battery, medical assessments, and collection of objective sleep data via actigraphy (1-week timeframe). All 172 CGs had a baseline assessment, 133 were assessed at post-treatment, 112 were assessed at 6-month follow-up, and 88 were assessed at 12-month follow-up.

2.2 Sample and Setting

The samples of Study 1 and Study 2 were comprised of non-overlapping cohorts of individuals aged 55 years or older providing in-home care to a spouse with Alzheimer's Disease. Study 1 also included a smaller group (n=60) of non-caregiver controls that allowed for analyses assessing differences between CGs and non-CGs.

Inclusion and exclusion criteria

Participants in these studies were CGs of a spouse with Alzheimer's disease (AD), 55 years or older at the time of enrollment, providing at least 20 hours of in-home care per week. Study 2 featured an additional inclusion criterion of CGs screening positive for mild depressive symptoms (PHQ-2 administered by phone). CGs in Study 2 were excluded if they had prior participation in a behavioral CG intervention, were diagnosed with a terminal illness, demonstrated cognitive impairment, had severe hypertension (>200/120 mm Hg), received treatment with anticoagulants, or had a history of myocardial infarction or stroke. Certain medications have effects on various biomarkers, and thus were assessed in order to control for these medications in statistical analyses.

2.3 Measures

The measures used to assess the primary variables of interest (i.e., sleep and markers of CVD risk) in Study 1 and Study 2 largely overlapped except for the addition of the Insomnia Severity Index (ISI) in Study 2. Descriptions of the assessments and data acquisition techniques relevant to this dissertation follow.

Descriptive/Background Characteristics

Interviewers gathered information on: 1) age, gender, years of caregiving, education, financial status, and occupation of the CG; 2) medical history, which included a review of systems, medical diagnoses, (e.g., cardiovascular, diabetes, hypertension, etc.), psychiatric history, drug/alcohol history, hospitalizations, and medication use over the two months prior to enrollment, including over-the-counter medications; 3) health factors potentially associated with physiologic outcomes, including height and weight for body mass index (BMI); 4) use of formal services (e.g., support groups, individual counseling), 5) amount of CG engagement in a variety of health and health risk behaviors, including smoking history, alcohol consumption, weight maintenance, physical activity, and diet.

Intima Media Thickness (IMT)

A Terason T3000 (Teratech, Burlington, MA) high resolution portable ultrasound machine was used to collect high quality B-mode images of the far wall of the common, bifurcation and internal carotid artery segments from 2 standardized interrogation angles for each vessel. The interrogation angles differed slightly between studies (Study 1 -Right: 180° and 120°, Left: 180° and 240°; Study 2 - Right: 150° and 90°, Left: 210° and 270°). The maximum IMT value was chosen as recommended by Allan et al. (1997) who argued that examining the maximum IMT is preferable to the mean IMT of all segments because examining the mean could

underestimate atherosclerotic risk for those with high measurements in one particular segment, but not necessarily in others. Further details of the methods for obtaining IMT are outlined by Roepke and colleagues (2012). Increased IMT has been shown to be associated with increased Framingham risk factors and prevalence of CVD (Polak et al., 2010).

Endothelium-dependent Flow Mediated Dilation (FMD)

Ultrasound recording (Celermajer et al., 1992) of the right brachial artery FMD was performed in duplex mode 4 hours postprandial, between 11:00 a.m. and 1:00 p.m. Participants were asked to refrain from exercise, caffeine, and smoking for 12 hours prior to testing. However, because their common use in the elderly makes it impractical (and potentially unsafe) to require discontinuation of vasoactive medications we instead documented their use and dosage and can add these data to the statistical models on FMD outcomes. The brachial artery was scanned using a 5-12Mhz linear-array probe holder and attached to the Terason T3000. The occlusion cuff was then inflated to 50 mmHg above SBP for five minutes and then released. An analysis of beat-to-beat end-diastolic images was performed with our custom-made software. The FMD response to release of the cuff was normalized to minimize the effect of different vessel diameters. First, artery diameter (D) and mean linear blood velocity (V_{avg}), obtained by ultrasound in duplex mode, were used to calculate shear rate (γ) for 90 s post-occlusion: $\gamma(s^{-1}) = 4(V_{avg}\left(\frac{cm}{s}\right))/D(cm)$. Then, vasodilation was normalized for shear rate by dividing FMD (%) by cumulative shear rate, expressed as the AUC, up to the point of maximal dilation (Pyke & Tschakovsky, 2005). A meta-analysis of 23 studies found that FMD was inversely associated with future CVD events (Ras, Streppel, Draijer, & Zock, 2013).

Blood Pressure and Baroreflex

BRS was determined from 5-minute noninvasive continuous beat-to-beat pulse rate and blood pressure recordings obtained in supine resting position with a Finometer PRO monitoring system (Finapres Medical Systems, Amsterdam, The Netherlands). The BRS and baroreflex efficiency index (BEI) were measured by the sequence method (Bertinieri et al., 1988). We used our custom-made LabVIEW software to calculate the slope of spontaneous blood pressure and heart rate changes. The BRS was calculated as the average of all linear regression slopes over the full 5 minutes.

Markers of CVD Risk and SAM Arousal

We used a panel of validated biomarkers shown in the literature and/or our preliminary data to reflect the CVD biomarker mediators of CG stress and SAM arousal noted in our theoretical model. The CVD biomarker mediators include IL-6, CRP, and tumor necrosis factor alpha (TNF-α) as indicators of systemic inflammation; vWF as a soluble endothelial activation/damage marker; and D-dimer and plasminogen activator inhibitor-1 (PAI-1) antigen, both markers of a procoagulant shift. The SAM arousal markers include urinary epinephrine and norepinephrine. All of these biomarkers have shown associations with increased risk for CHD independent of other cardiovascular risk factors (Zakai et al., 2017; Tuomisto, Jousilathi, Sundvall, Pajunen, & Salomaa, 2006; Cooney, Dudina, O'Callaghan, & Graham, 2007;

At each assessment approximately 40 ml of venous blood was drawn. For D-dimer, PAI-1, and vWF, blood was drawn into plastic syringes containing 3.2% sodium citrate (9:1, v/v); the first 2 ml were discarded. Minimal tourniquet pressure was used. For CRP, IL-6, and TNF-α as well as routine chemistry panel (including lipids and blood glucose) EDTA blood were used. Subsequently, samples were centrifuged twice for 15 minutes at 2000 x g at room temperature.

Obtained plasma was immediately stored in plastic tubes at –80ºC in aliquots of 1 ml until further processing. Urine samples for catecholamines were collected between 9 and 12 AM. We avoided collecting the first void morning sample to obtain a sample of representative daytime values.

All samples from a particular study participant were typically assayed together with a single lot number of reagents and consumables employed by a single laboratory technician who was blinded to participant identifiers. Concentrations of TNF-α, CRP, and IL-6 (Meso Scale Discovery) and vWF antigen, PAI-1 antigen, and D-dimer (Asserachrom; Stago, Asnières, France) were determined via enzyme-linked immunosorbent assay (ELISA). Intra-assay coefficients of variation are <5%; inter-assay coefficients of variation are <7%; assay sensitivities are excellent. Urine catecholamine values were normalized to creatinine concentration, which allowed comparison of catecholamine levels without correction for sex or body mass. Concentrations of norepinephrine and epinephrine were determined using a Catechol-O-methyltransferase- based (COMT) radioenzymatic assay with a preconcentration step which extracts catecholamines from urine and concentrates them in 0.1 ml of dilute acid (Kennedy & Ziegler, 1990). The assay is 10 times as sensitive as prior methods. The assay removes components of urine such as Ca2+ that inhibit the COMT assay. Inter- and intra-assay coefficients of variation are <10%.

Sleep and CAR Variables

Subjective measures of sleep were collected in both studies via the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and, for study 2, the Insomnia Severity Index (ISI; Bastien et al., 2001) was added. The PSQI is a seven-component self-report questionnaire assessing various aspects of sleep quality including typical time in bed, sleep onset latency, sleep

duration, use of sleep aids, specific sleep disturbances, daytime sleepiness, and daytime impairment. A score >5 suggests poor sleep. The scale has demonstrated good internal consistency (Cronbach's alpha = 0.83) and has been validated in older populations (Alessi et al., 2008). The ISI consists of seven items that assess problems with several aspects of sleep (e.g., sleep onset, sleep maintenance, satisfaction with sleep, interference with daily functioning) in the last 2 weeks. A score of 0-7 indicates no clinically significant insomnia, 8-14 suggests subthreshold insomnia symptoms, 15-21 indicates clinically significant insomnia (moderately severe), and scores of 22-28 indicate severe insomnia. The ISI has been shown to have good internal consistency and is also a valid and sensitive measure of changes in perceived sleep difficulties related to treatment (Bastien et al., 2001).

Objective measures of sleep were recorded with the Actiwatch wrist actigraph (Philips/Respironics). The Actiwatch is a small, digitally integrated measure of gross motor activity, equipped with a highly sensitive accelerometer. We recorded data over a specified period (i.e., 3 consecutive 24-hour periods for Study 1, 7 consecutive 24-hour periods for Study 2), during which time all participants recorded sleep information in a sleep log which was used to edit the data. Activity data were scored with the Actiware software to calculate total sleep time (TST, the total amount of time an individual is asleep at night) and percent sleep (a ratio of the time spent asleep between the actigraphy scored sleep onset and final wake time). Percent sleep is a different construct from sleep efficiency, as percent sleep only included the window between sleep onset and final wake time and does not include sleep onset latency or time awake in bed following final awakening.

Circadian activity rhythms (CAR) were computed based on activity levels recorded with actigraphy and analyzed by fitting each participant's epoch-by-epoch activity data to an extended

cosine model (Marler, Gehrman, Martin, and Ancoli-Israel, 2006), that generated multiple circadian rhythm variables. These variables included amplitude (the maximum activity value minus the minimum activity value), minimum (lowest activity value), mesor (value half-way between maximum and minimum), slope (an indicator of how quickly activity changes from minimum to maximum), acrophase (time of day of the peak of the curve), up-mesor (time of day when participants' activity level shifted from below the mesor to above the mesor), down-mesor (time of day when participants' activity level shifted from above the mesor to below the mesor), width ratio (fraction of the day that activity is above the mesor), r^2 (the reduction in squared error from using this model to summarize the data compared to using the mean), F (an adjustment to r^2 accounting for number of observations and parameters in the model), and $F_{improve}$ (the reduction in variance from using the sigmoidally transformed cosine curve in place of the cosine curve to summarize data and predict future values, adjusted for the number of observations and the number of parameters in the model). The values of r^2, F, and $F_{improve}$ can all be interpreted as larger values indicating stronger (i.e., more consistent/robust) circadian activity rhythms. Clinically, circadian activity rhythms give an indication of not only the consistency or strength of an individual's activity patterns across the day but also of the timing. Prior research broadly supports that individuals with more robust circadian activity rhythms and individuals with earlier wake and activity times (i.e., more 'morningness') have improved health outcomes, including less incidence of illnesses like dementia and cancer (Tranah et al., 2010).

Depressive Symptoms and Positive and Negative Affect

The Center for Epidemiologic Studies Depression scale (CES-D; Radloff, 1977) is a 20-item scale widely used to assess symptoms of depression. The CES-D has excellent validity and reliability with older adults and has acceptable sensitivity and specificity when used as a

screening tool for case finding in population studies. In addition, the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was administered. The PANAS has demonstrated good reliability and is valid for use in elderly populations (Kercher, 1992).

Caregiver Stress

Data regarding caregiver stress were collected through multiple sources. The stresses of caregiving were assessed via the Revised Memory and Behavior Checklist (RMBC; Teri et al., 1992) and Zarit Burden Inventory – Short Form (ZBI-12; Bédard, Squire, Dubois, Lever, & O'Donnell, 2001). The RMBC is a 24-item questionnaire completed by the CG assessing the frequency of problematic care recipient behaviors and a rating of the CG's reaction to those behaviors. The ZBI-12 is a 12-item questionnaire completed by the CG assessing potential burden associated with caregiving (e.g., 'do you feel stressed between caring for your relative and trying to meet other responsibilities?'). To assess the severity of dementia in the care recipient our research nurse completed the Clinical Dementia Rating form (CDR; Hughes, Berg, Danziger, Coben, & Martin, 1982). Years of caregiving has been previously demonstrated to be related to cardiovascular outcomes such as FMD and IMT (Mausbach et al., 2010; Roepke et al., 2012) and was regarded as another measure of caregiver burden.

Physical Activity

The Rapid Assessment of Physical Activity (RAPA; Topolski et al., 2006) has been demonstrated to be a psychometrically sound measure for use in elderly population, and physical activity was considered as a potential mediator of treatment response and thus shall be controlled for in statistical analyses.

2.4 Intervention Methods

Behavioral Activation

Our BA intervention was based upon the theories of Lewinsohn, Jacobson, and others (Jacobson, Martell, & Dimidjian, 2001; Hopko, Lejuez, Ruggiero, & Eifert, 2003; Lewinsohn & Libet, 1972; Lewinsohn & Graf, 1973), which emphasize self-monitoring as an aid for increasing one's engagement in self-reinforcing activities while simultaneously reducing negative avoidant coping responses. In order to allow participants to target behaviors that are important to them and for the therapist to tailor activities for each participant, BA utilizes an individually based format. The intervention consisted of 6 total face-to-face sessions lasting 60 minutes each. The emphases of the 6 sessions are outlined below.

Session 1: Recognizing Negative Moods/Creating a Healthy Environment - The first session was focused on understanding depressive symptoms and their effect on one's life (e.g., health, behaviors, etc.). Discussions focused on: a) identifying depressive symptoms, b) how to use self-monitoring to track existing engagement in pleasant events, and c) how to create an environment that supports "Healthy Behavior" (i.e., that which promotes positive moods) and minimizes behavior leading to negative moods (e.g., avoidance). Therapists provided examples on how to complete homework assignments which included self-monitoring worksheets.

Session 2: Life Goal Assessment/ Activity Identification – The participant and counselor first reviewed the homework activity from the previous session and discussed the participant's current engagement in activities. Then, the participant was provided with a structured group of tasks to help identify treatment goals, including a) selecting new activities from several life domains (e.g., hobbies) that may increase access to rewarding experiences, and b) creating an activity hierarchy which helped participants start with achievable activities and gradually move to more difficult ones. Further, the "activity hierarchy" helped maintain motivation by taking a stepwise goal-setting approach while helping reduce barriers to treatment compliance.

Sessions 3-6: Behavioral Activation/Planning for the Future – Over the remaining sessions, participants tracked their engagement in the activities they selected during the first sessions. Participants completed a master activity log which summarized the total number of times the individual engaged in selected activities. At the end of each week, participants completed a weekly behavior checkout, which helped provide graphic feedback on how well participants stayed on-track with their activity goals. Based on this feedback, participants could work with their therapist to continue identifying barriers and alter goals to make achievement more likely. Participants also graphed their moods to monitor the effects of engaging in reinforcing activities. Finally, therapists encouraged participants to continue self-monitoring and updating activity goals so that benefits can be maintained over longer periods of time.

Information-Support (IS)

Our IS condition permitted us to address the question of whether contact with participants resulted in change in our outcomes. The inclusion of this comparison group was also important as a method for disentangling the effects of self-report bias, historical trends, and maturation vis-à-vis the effects of the intervention. Participants randomized to this condition received six 60-minute face-to-face sessions that provided a supportive environment to address problems. That is, our IS intervention contained common therapeutic components such as empathy and active listening. Participants were given the opportunity to report their experiences over the previous week and reveal any concerns they had during that time. In addition to support, our team developed a comprehensive resource guide containing materials on AD, coping with specific stresses prevalent in caregiving, and services available for CGs in San Diego County (i.e., information). Caregivers were therefore able to choose information most relevant to their current circumstances and discuss this with their therapist during the sessions. Currently, standard care

(i.e., “usual care”) provided to caregivers from community agencies is information (e.g., brochures) and support (e.g., support groups). Freedland et al. (2011) points out that behavioral medicine trials often make use of “enhanced usual care” control conditions because they are advantageous in dealing with ethical and methodological concerns while increasing the external validity of findings. Our IS condition closely approximated the care currently received by CGs but was individualized to the caregiver and offered via face-to-face meetings with therapists and can be considered an enhanced version of the current “usual care” provided to CGs. Demonstrating significant effects of BA vs. IS would therefore enhance the external validity of our findings by suggesting that CGs receiving “usual care” in the community would benefit from receipt of the BA protocol.

2.5 Data Analyses

Numerous characteristics of sleep and their associations with several markers of CVD and vascular pathology were analyzed. Primary independent variables of interest included subjective summaries of sleep quality (i.e., total ISI and PSQI scores), actigraphy measures of total sleep time (TST) and percent sleep, and several CAR variables that were derived from actigraphy. Primary dependent variables of interest included carotid IMT, FMD, mean arterial pressure (MAP), baroreflex sensitivity (BRS), heart rate (HR), and biomarkers of CVD risk (i.e., IL-6, CRP, TNF-α, vWF, D-dimer, PAI-1, norepinephrine [NE], epinephrine [EPI]).

Statistical methods varied for each aim.

Aim 1. **Examine cross-sectional associations between subjective, objective, and circadian sleep measures and markers of CVD risk in Alzheimer’s caregivers.** The goal of Aim 1 was to assess the cross-sectional association between sleep measures (i.e., total ISI score, total PSQI score, TST, Sleep Percent, CAR variables) and markers of CVD risk (i.e., IMT, FMD,

MAP, BRS, HR, IL-6, CRP, TNF-α, vWF, D-dimer, PAI-1, NE, EPI) using baseline data. For these analyses, data from both studies were combined whenever possible in order to increase power of analyses. However, Study 1 did not administer the ISI and data from Study 2 does not include FMD data. Significant differences in study characteristics between studies 1 and 2 were not anticipated. Given that the inclusion/exclusion criteria of each study were nearly identical, it was thought that data from each study could be aggregated without issue. To account for observed significant differences, individual analyses were conducted both for the aggregated data and for each individual sample if the analysis included one of the variables with significant differences between study samples.

Associations between sleep parameters and markers of CVD risk were evaluated first using Pearson product-moment correlations to identify potentially significant linear relationships ($\alpha \leq .05$). Multiple linear regression was used to test these associations controlling for relevant covariates. Age, sex, BMI, various measures of caregiver burden (RMBC, CDR, ZBI, and years caregiving), and physical activity assessed with the RAPA were considered as potential covariates for the models in Aim 1. Separate models were estimated for each sleep parameter/CVD risk marker pair showing significant correlations. Prior to model construction, the data were assessed to see if obvious outliers existed (i.e., values outside of possible ranges or clear data entry errors); no outliers were identified, and no data were removed. Many of the biomarker data exhibited right-skewed distributions. Although the assumptions of linear regression stipulate that data are normally distributed; in large samples, linear regression has been shown to be robust to violations of this assumption (Schmidt and Finan, 2018). Therefore, no variable transformations were calculated. Hypothesis 1: It was hypothesized that subjective and objective sleep parameters and CAR variables would show significant associations with

various markers of CVD risk and vascular pathology, however no hypotheses were made regarding specific outcome variables. Significant regression coefficients for the sleep predictors (i.e., total ISI score, total PSQI score, TST, sleep percent, and CAR variables) in the above referenced multiple regression models provided support for this hypothesis.

Power analyses were conducted using G-Power (Faul, Erdfelder, Lang, & Buchner, 2007) to assess the power of *t*-tests from one group linear bivariate regression size of slopes, which was appropriate given the approach outlined in Aim 1 (multiple linear regression comparing sleep parameters and CVD markers). Effect sizes from previous research on associations between TST and biomarkers of inflammation (CRP, $\beta = 0.88$; TNF-α, $\beta = 0.88$; IL-6, $\beta = 0.91$; Patel et al., 2009) were used in power calculations. With a combined sample size of 295, this study is well powered to detect the purported effect sizes ($P = 0.95$). These power calculations only cover a small subset of the proposed data analyses, and only examine one of the proposed predictors (i.e., TST). Power was significantly lower for analyses in which data from only one of the two studies is available (i.e., analyses including ISI scores or FMD) or instances of missing data (e.g., CAR data).

Aim 2. **Observe longitudinal associations between sleep measures and markers of CVD in Alzheimer's caregivers.** Using data from Study 1, the goal of Aim 2 was to observe longitudinal associations between sleep parameters (i.e., PSQI scores, TST, and sleep percent) and CVD risk markers (i.e., IMT, FMD, MAP, BRS, HR, IL-6, CRP, TNF-α, vWF, D-dimer, PAI-1, NE, EPI). CAR data were not tested in these analyses due to insufficient CAR data for visits beyond baseline. Multilevel models (i.e., hierarchical linear models) were constructed to observe linear relations of markers of CVD risk and time. Grand-mean centered sleep variables, caregiver status, and the interaction of these variables were included at level 2 to observe whether they had

a significant impact on cardiovascular outcomes over time. Multilevel modeling allows for analysis of nested data, here repeated measures nested within individuals. Because multilevel models give heavier weight to participants with more waves of data, the data was first analyzed to determine if missing data is missing at random (MAR). Age, sex, BMI, physical activity (assessed by RAPA), and various indicators of caregiver stress (RMBC, CDR, ZBI, and years caregiving) were considered as potential covariates for these models. All these variables were grand-mean centered and examined at level 2 to determine if they had a significant impact on these linear associations (i.e., intercepts or slopes). Separate models were assessed for each sleep parameter/CVD risk marker pair. For each association, models were constructed using a stepwise approach including an intercept-only model, random-coefficient regression model, and intercepts- and slopes-as-outcomes model. Variables were retained in the model at each step if they improved overall model fit. Model fit was determined by examining fit indices of AIC, BIC, and log likelihood. A model fit was deemed to be improved if inclusion of a variable resulted in improvements in at least two of these three indices. An example of the final intercepts- and slopes-as-outcomes model without covariates follows. Subscripts *i* and *t* refer to subjects and timepoints respectively:

Level 1 Model:

$$Y_{it} = b_{0i} + b_{1i}(X_{it}) + \varepsilon_{it}$$

Level 2 Models:

$$b_{0i} = \gamma_{00} + \gamma_{01}C_{1i}^{*} + \gamma_{02}C_{2i} + \gamma_{03}C_{1i}^{*}C_{2i} + u_{0i}$$
$$b_{1i} = \gamma_{10} + \gamma_{11}C_{1i}^{*} + \gamma_{12}C_{2i} + \gamma_{13}C_{1i}^{*}C_{2i} + u_{1i}$$

This yields a combined equation of:

$$Y_{it} = \gamma_{00} + \gamma_{01}C_{1i}^{*} + \gamma_{02}C_{2i} + \gamma_{03}C_{1i}^{*}C_{2i} + u_{0i} + \gamma_{10}X_{it} + \gamma_{11}C_{1i}^{*}X_{it} + \gamma_{12}C_{2i}X_{it} + \gamma_{13}C_{1i}^{*}C_{2i} + u_{1i}X_{it}^{*} + \varepsilon_{it}$$

In these models, Y_{it} represents the cardiovascular outcome for each participant *i* at each timepoint *t*. The level 2 equations predict values for the intercepts and slopes of the linear associations including the effects of the grand-mean centered sleep variable (C_{1i}^{*}), caregiver status (C_{2i}), and their interaction. Here, γ_{11} (i.e., the effect of the included sleep variable on the slope of the cardiovascular outcome over time) and γ_{13} (the interaction of the sleep variable and CG status on the slope) are of particular interest. Hypothesis 2a: It was hypothesized that sleep disturbance would predict greater CVD risk over time as reflected by increased markers of CVD and vascular pathology. Hypothesis 2b: It was hypothesized that the associations between sleep/CAR variables and markers of CVD risk would be more severe for caregivers compared to non-caregivers. Again, hypotheses were not made for specific parameters. Significant parameter estimates ($\alpha \leq .05$) for γ_{11} and γ_{13} will support the hypothesis.

Power analyses were not attempted for these multivariate, longitudinal analyses. The complexities introduced by within-subject correlation, number of repeated assessments, and level of missing data can all affect the estimations for required sample sizes (Lu et al., 2013).

Aim 3. **Test the ability of a brief BA intervention to improve sleep in Alzheimer's caregivers.** Data from Study 2 was analyzed to determine the efficacy of a brief BA intervention for improving sleep parameters (i.e., ISI scores, PSQI scores, TST, percent sleep, CAR variables) compared to our IS condition representing "enhanced" usual care. Multilevel models were used to determine if treatment condition was related to improvement in subjective/objective sleep and CAR variables. These analyses followed a similar structure to the analyses for aim 2, however sleep variables were regarded as the outcome of interest and treatment condition was included at level 2 to determine if the linear relationships of sleep variables over time differed by treatment

condition. An example of the final intercepts- and slopes-as-outcomes model without covariates follows. Subscripts *i* and *t* refer to subjects and timepoints respectively:

Level 1 Model:

$$Y_{it} = b_{0i} + b_{1i}(X_{it}) + \varepsilon_{it}$$

Level 2 Models:

$$b_{0i} = \gamma_{00} + \gamma_{01}C_{1i} + u_{0i}$$
$$b_{1i} = \gamma_{10} + \gamma_{11}C_{1i} + u_{1i}$$

This yields a combined equation of:

$$Y_{it} = \gamma_{00} + \gamma_{01}C_{1i} + u_{0i} + \gamma_{10}X_{it} + \gamma_{11}C_{1i}X_{it} + u_{1i}X_{it} + \varepsilon_{it}$$

Hypothesis 3: It was hypothesized that CGs in the BA treatment condition would exhibit greater improvement in subjective/objective sleep and CAR variables compared to those in the IS condition. Significant parameter estimates for γ_{11} (i.e., the effect of treatment condition on the associations between sleep outcomes and time) were identified to support the hypothesis.

In addition to multilevel models, pre-post ANOVAs were also analyzed for each sleep variable by treatment condition to determine if there was a significant difference between conditions specifically from pre-treatment to post-treatment. A statistically significant *F* value ($\alpha \leq .05$) indicated support for the hypothesis.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Brent Mausbach, Ph.D., Sonia Ancoli-Israel, Ph.D., Igor Grant, M.D., Jonathan Helm, Ph.D., and Vanessa Malcarne, Ph.D. The dissertation author was the primary investigator and author of this material.

Chapter 3: Results

3.1 Aim 1: Cross-sectional Associations between Sleep Variables and Markers of CVD Risk

The goal of aim 1 was to investigate the cross-sectional associations between subjective, objective, and circadian sleep measures and markers of CVD risk and vascular pathology.

Baseline Sample Characteristics

Baseline sample characteristics for each study sample and the combined sample can be found in Table 1. The combined sample of 295 caregivers includes 75 men (25.4%) and 220 women, overwhelmingly white (89.6%). Caregivers ranged in age from 54.7 to 93.4 years old (M = 73.93 years, SD = 7.98). Participants had been caregiving for an average of 4.52 years at the time they entered the study (SD = 3.41).

To assess the similarity between the two study samples, independent samples t-tests were conducted for each variable of interest grouped by study to examine significant differences in means and Levene's test for equality of variances. Results of these tests appear in Table X. Levene's test revealed that the following variables have significantly different variances across the two studies: CRP ($F_{1, 263} = 4.458$, $p = .036$), TNF-α ($F_{1, 262} = 86.930$, $p < .001$), EPI ($F_{1, 135} = 3.895$, $p = .050$), NE ($F_{1, 135} = 22.442$, $p < .001$), D-Dimer ($F_{1, 266} = 99.519$, $p < .001$), CAR – Amplitude ($F_{1, 159} = 4.381$, $p = .038$), CAR – R squared ($F_{1, 159} = 5.246$, $p = .031$), CAR – F statistic ($F_{1, 159} = 5.246$, $p = .023$), RMBC – React ($F_{1, 276} = 6.430$, $p = .012$), IMT-CCA ($F_{1, 219} = 9.074$, $p = .003$), IMT-BIF ($F_{1, 186} = 6.565$, $p = .011$), and IMT-INT ($F_{1, 192} = 10.212$, $p = .002$). Independent samples t-tests found significant mean differences in several variables. Participants in study 1 (longitudinal study) had significantly higher mean CDR total score ($t(286) = 3.677$, $p < .001$), TNF-α ($t(129.528) = 15.586$, $p < .001$), D-Dimer ($t(141.035) = 6.332$, $p < .001$), MAP ($t(269) = 2.134$, $p = .034$), CAR – Mesor ($t(161) = 2.270$, $p = .025$), and CAR – R squared ($t(54.435) = 3.140$, $p = .003$). Participants in study 2 (intervention study) had significantly higher

mean RMBC – Reaction scores ($t(277.974) = -11.710$, $p < .001$), CES-D total score ($t(289) = -4.097$, $p < .001$), negative affect ($t(293) = -4.213$, $p < .001$), IMT-CCA ($t(174.210) = -11.092$, $p < .001$), IMT-BIF ($t(178.021) = -10.656$, $p < .001$), and IMT-INT ($t(161.687) = -7.431$, $p < .001$). Pearson product-moment correlations between the sleep predictor variables and the vascular outcome variables for the combined sample can be found in Table 3.

Regression Analyses of Baseline Associations

Using the combined study sample, regression models were explored for each significant correlation observed in Table 3. The same covariates were explored for every model, including age, sex, BMI, RAPA scores, years caregiving, RMBC scores (for both Frequency and Reaction scales), and CDR total score. Covariates were added to regression models in a stepwise fashion and adjusted r^2 was compared in each model to determine best model fit. Covariates that improved model fit were retained in the final model regardless of whether they showed statistically significant associations with the cardiovascular outcomes while covariates that did not improve model fit were discarded. Models were also fit for each study data individually if any of the variables of interest exhibited inequality of means or variances across the two studies.

ISI and D-Dimer. ISI data were only collected during study 2; results of the regression using ISI scores to predict D-Dimer are presented in Table 4. In the optimal model, BMI alone was a significant predictor of D-Dimer levels ($\beta = 6.378$, $t(115) = 2.619$, $p = .010$). Main effects of ISI score, RAPA, and RMBC-Frequency were not statistically significant, but inclusion of these variables did improve model fit indices. Potential covariates of age, sex, RMBC-React, years caregiving, and CDR score were explored, but did not improve model fit.

These results suggest that when adjusting for relevant covariates, ISI score is not significantly associated with D-Dimer at baseline. However, BMI was a significant predictor of

D-Dimer, indicating that caregivers with higher BMI at baseline exhibited higher levels of circulating D-Dimer.

Amplitude and Baroreflex Sensitivity. Results of the regression using CAR-Amplitude to predict BRS are presented in Table 5. For the combined sample, main effects of CAR-Amplitude, BMI, and RAPA were not statistically significant, but inclusion of these variables did improve overall model fit. RMBC-Frequency was a significant predictor of BRS ($\beta = 0.111$, $t(97) = 2.855$, $p = .005$), such that patients reporting increased frequency of care recipient problem behaviors exhibit higher BRS at baseline. Other covariates were explored but did not improve model fit and were not included in the final regression model.

Due to the noted inequivalence of the variance of CAR-Amplitude across studies, regression models were explored for each study individually. However, this exploration revealed that only 14 of the 111 cases originated from study 1 due to a high amount of missing CAR data. The results of the regression examining study 2 alone are not significantly different from the results of the combined sample.

These results suggest that when adjusting for relevant covariates, amplitude is not significantly associated with BRS at baseline. However, the frequency of reported care recipient problem behaviors was a significant predictor of BRS at baseline; caregivers reporting more frequent problem behaviors exhibited slightly higher BRS.

Minimum and Baroreflex Sensitivity. Results of the regression using CAR-Minimum to predict BRS are presented in Table 6. Main effects of CAR-Minimum, BMI, and RAPA were not statistically significant, but inclusion of these variables did increase overall model fit. RMBC-Frequency was a significant predictor of BRS ($\beta = 0.112$, $t(106) = 2.879$, $p = .005$), such that patients reporting increased frequency of care recipient problem behaviors exhibit higher

BRS at baseline. Other covariates were explored but did not improve model fit and were not included in the final regression model.

These results suggest that when adjusting for relevant covariates, minimum activity level is not significantly associated with BRS at baseline. Again, the frequency of reported care recipient problem behaviors was a significant predictor of BRS at baseline; caregivers reporting more frequent problem behaviors exhibited slightly higher BRS.

Up-mesor and Baroreflex Sensitivity. Results of the regression using CAR-Upmesor to predict BRS are presented in Table 7. CAR-Upmesor was a significant predictor of BRS (β = -1.163, $t(105)$ = -2.784, p = .006). Caregivers with later start times for significant daytime activity showed impaired BRS. Significant main effects were present also for BMI (β = -0.196, $t(105)$ = -2.273, p = .025) and RMBC-Frequency scores (β = 0.133, $t(105)$ = 3.378, p = .001). Main effects of sex and RAPA were not statistically significant, but inclusion of these variables did improve overall model fit. Other covariates were explored but did not improve model fit and were not included in the final regression model.

These results suggest that when adjusting for relevant covariates, time of day where caregivers transition from low to high activity is significantly associated with BRS at baseline such that caregivers with later times to initiate high activity exhibit impaired BRS. Additionally, caregivers with higher BMI showed impaired BRS at baseline while caregivers reporting more frequent problem behaviors exhibited slightly higher BRS.

Width Ratio and Baroreflex Sensitivity. Results of the regression using CAR-Width Ratio to predict BRS are presented in Table 8. In the combined sample, main effects of CAR-Width Ratio and RAPA were not statistically significant, but inclusion of these variables did improve overall model fit. RMBC-Frequency (β = 0.113, $t(106)$ = 2.889, p = .005) and BMI (β =

-0.183, $t(106) = -2.099$, $p = .038$) were significant predictors of BRS such that patients reporting increased frequency of care recipient problem behaviors exhibit higher BRS and patients with higher BMI's experienced impaired BRS at baseline. Potential covariates of age, sex, RMBC-React, years caregiving, and CDR score were explored but did not improve model fit.

These results suggest that when adjusting for relevant covariates, the amount of time caregivers spend above their middle activity level is not significantly associated with BRS at baseline. Consistent with previous results, caregivers with higher BMI showed impaired BRS at baseline while caregivers reporting more frequent problem behaviors exhibited slightly higher BRS.

CAR R^2 and Baroreflex Sensitivity. Results of the regression using CAR-R^2 to predict BRS are presented in Table 9. CAR-R^2 was a significant predictor of BRS even when controlling for relevant covariates ($\beta = 9.973$, $t(106) = 2.270$, $p = .025$). Caregivers with "stronger" (i.e., more consistent) circadian rhythms exhibit better BRS at baseline. A significant main effect was present also for RMBC-Frequency ($\beta = 0.111$, $t(106) = 2.896$, $p = .005$), whereby caregivers reporting more frequent care recipient problem behaviors exhibited better BRS at baseline. Main effects of BMI and RAPA were not statistically significant, but inclusion of these variables did increase overall model fit. Potential covariates of sex, age, RMBC-React, years caregiving, and CDR score were explored but did not result in improved model fit.

Due to the noted inequivalence of the means and variances of CAR-R^2 across studies, regression models were explored for each study individually. However, this exploration revealed that only 14 of the 111 cases originated from study 1 due to a high amount of missing CAR data. The results of the regression examining study 2 alone are not significantly different from the results of the combined sample.

These results suggest that when adjusting for relevant covariates, the robustness of circadian rhythm is significantly associated with BRS at baseline such that caregivers with stronger circadian activity rhythms have better BRS. Consistent with previous results, caregivers reporting more frequent problem behaviors exhibited slightly higher BRS.

CAR F statistic and Baroreflex Sensitivity. Results of the regression using CAR-F statistic to predict BRS are presented in Table 10. CAR- F statistic was a significant predictor of BRS even when controlling for relevant covariates ($\beta = 0.001$, $t(106) = 1.990$, $p = .049$). Caregivers with "stronger" (i.e., more consistent) circadian rhythms exhibit improved BRS at baseline. A significant main effect was present also for RMBC-Frequency ($\beta = 0.100$, $t(106) = 2.562$, $p = .012$). Main effects of BMI and RAPA were not statistically significant, but inclusion of these variables did increase overall model fit. Potential covariates of sex, age, RMBC-React, years caregiving, and CDR score were explored but did not result in improved model fit.

Due to the noted inequivalence of the means and variances of CAR-F statistic across studies, regression models were explored for each study individually. However, this exploration revealed that only 14 of the 111 cases originated from study 1 due to a high amount of missing CAR data. The results of the regression examining study 2 alone are not significantly different from the results of the combined sample.

These results suggest that when adjusting for relevant covariates, the robustness of circadian rhythm is significantly associated with BRS at baseline such that caregivers with stronger circadian activity rhythms have better BRS. Consistent with previous results, caregivers reporting more frequent problem behaviors exhibited slightly higher BRS.

CAR $F_{improve}$ and Baroreflex Sensitivity. Results of the regression using CAR-$F_{improve}$ to predict BRS are presented in Table 11. CAR-$F_{improve}$ was a significant predictor of BRS even

when controlling for relevant covariates (β = 0.002, t(106) = 2.036, p = .044). Caregivers with "stronger" (i.e., more consistent) circadian rhythms exhibit improved BRS at baseline. A significant main effect was present also for RMBC-Frequency (β = 0.108, t(106) = 2.792, p = .006). Main effects of BMI and RAPA were not statistically significant, but inclusion of these variables did increase overall model fit. Potential covariates of sex, age, RMBC-React, years caregiving, and CDR score were explored but did not result in improved model fit.

These results suggest that when adjusting for relevant covariates, the robustness of circadian rhythm is significantly associated with BRS at baseline such that caregivers with stronger circadian activity rhythms have better BRS. Consistent with previous results, caregivers reporting more frequent problem behaviors exhibited slightly higher BRS.

Slope and TNF-α. Results of the regression using CAR-Slope to predict TNF-α are presented in Table 12. Main effects of CAR-Slope, age, and BMI were not statistically significant, but inclusion of these variables did improve overall model fit. RMBC-Frequency (β = 0.075, t(133) = 3.844, p < .001) and RMBC-React (β = -0.102, t(133) = -6.198, p < .001) were both significant predictors of TNF-α such that patients reporting increased frequency of care recipient problem behaviors exhibit higher TNF-α and patients who reported more reaction to problem behaviors reported lower levels of TNF-α at baseline. Potential covariates of sex, years caregiving, and CDR score were explored but did not result in improved model fit.

Due to the noted inequivalence of both means and variances of TNF-α across the two studies, regressions were also fitted for each study individually yielding differing results. For study 1, the optimal model includes significant main effects of CAR-Slope (β = 0.055, t(34) = 3.118, p = .004) and CDR score (β = -2.026, t(34) = -2.855, p = .007). Age and years caregiving are included in the model due to increase in model fit but are not significant predictors of TNF-α.

In study 2; CAR-Slope, BMI, and RAPA were not significant predictors of TNF-α. There were significant main effects for caregiver age ($\beta = 0.032$, $t(100) = 3.647$, $p < .001$) and CDR score ($\beta = 0.237$, $t(100) = 1.992$, $p = .049$).

The results from study 1 suggest that the rate that caregivers transitioned from low to high activity was a significant predictor of TNF-α at baseline. Caregivers showing quicker changes from low to high activity levels showed higher levels of TNF-α. Total CDR score was also a significant predictor of TNF-α such that caregivers providing care to a spouse with more severe dementia exhibited lower levels of TNF-α. However, these results were not consistent in study 2 or the combined sample. In study 2, age and CDR score were the only significant predictors of TNF-α.

Amplitude and vWF. Results of the regression using CAR-Amplitude to predict vWF are presented in Table 13. The main effect of CAR-Amplitude was not statistically significant, but inclusion of this variable in the model did increase overall model fit. Caregiver age ($\beta = 3.618$, $t(142) = 3.342$, $p = .001$) and BMI ($\beta = 3.484$, $t(142) = 2.245$, $p = .026$) were both significant predictors of vWF such that caregivers who are older or have increased BMI exhibit higher levels of vWF at baseline. Potential covariates of sex, years caregiving, RAPA scores, RMBC scores, and CDR total score were explored but did not result in improved model fit.

Due to the noted inequivalence of variances of CAR-Amplitude across the two studies, regressions were also fitted for each study individually yielding differing results. However, this exploration revealed that only 39 of the 146 cases originated from study 1. The results of the regression examining study 2 alone are not significantly different from the results of the combined sample.

These results suggest that when adjusting for relevant covariates, amplitude is not significantly associated with vWF at baseline.

Mesor and vWF. Results of the regression using CAR-Mesor to predict vWF are presented in Table 14. There were significant main effects for CAR-Mesor (β = -113.555, t(142) = -2.380, p = .019), caregiver age (β = 3.120, t(142) = 3.002, p = .003), and caregiver BMI (β = 3.138, t(142) = 2.192, p = .030). Increased values of mesor were associated with significantly decreased vWF levels. Additionally, caregivers who are older or have higher BMI exhibit higher levels of vWF at baseline. Other potential covariates of sex, years caregiving, RAPA scores, RMBC scores, and CDR total score were explored but did not result in improved model fit.

Due to the noted inequivalence of means of CAR-Mesor across the two studies, regressions were also fitted for each study individually yielding differing results. However, this exploration revealed that only 39 of the 146 cases originated from study 1. The results of the regression examining study 2 alone are not significantly different from the results of the combined sample.

These results suggest that when adjusting for relevant covariates, mesor (i.e., the midpoint of the minimum and maximum activity levels) is significantly associated with vWF at baseline. Participants with higher mesors showed increased levels of vWF. Age and BMI were also significant predictors of vWF such that caregivers who are older or have higher BMI exhibit higher levels of vWF at baseline.

CAR-R^2 and vWF. Results of the regression using CAR-R^2 to predict vWF are presented in Table 15. The main effect of CAR-R^2 was not statistically significant, but inclusion of this variable in the model did increase overall model fit. Caregiver age (β = 3.398, t(142) = 3.220, p = .002) and BMI (β = 3.102, t(142) = 2.055, p = .042) were both significant predictors

of vWF such that caregivers who are older or have increased BMI exhibit higher levels of vWF at baseline. Potential covariates of sex, years caregiving, RAPA scores, RMBC scores, and CDR total score were explored but did not result in improved model fit.

Due to the noted inequivalence of both variances and means of CAR-R^2 across the two studies, regressions were also fitted for each study individually yielding differing results. However, this exploration revealed that only 39 of the 146 cases originated from study 1. The results of the regression examining study 2 alone are not significantly different from the results of the combined sample.

These results suggest that when adjusting for relevant covariates, robustness of the circadian activity rhythm is not significantly associated with vWF at baseline. Consistent with the previous analysis, age and BMI were also significant predictors of vWF such that caregivers who are older or have higher BMI exhibit higher levels of vWF at baseline.

Acrophase and PAI-1. Results of the regression using CAR-Acrophase to predict PAI-1 are presented in Table 16. There was a significant main effect for CAR-Acrophase (β = 5.518, $t(142)$ = -2.380, p = .019) as well as caregiver age (β = -1.008, $t(142)$ = 3.002, p = .003), BMI (β = 1.334, $t(142)$ = 2.192, p = .030), and physical activity as assessed by the RAPA (β = -3.795, $t(142)$ = 2.192, p = .030). The was no significant main effect of RMBC Reaction scores, but inclusion of this variable did increase overall model fit. Since acrophase represents the time of day when activity peaks, these results indicate that caregivers with a later circadian clock appear to exhibit increased PAI-1 levels. Additionally, caregivers who have increased BMI exhibit higher levels of PAI-1 while older caregivers and more physically active caregivers show lower levels of PAI-1 at baseline. Other potential covariates of sex, years caregiving, scores, RMBC-Frequency scores, and CDR total score were explored but did not result in improved model fit.

These results suggest that when adjusting for relevant covariates, acrophase is significantly associated with PAI-1 at baseline; caregivers with more delayed circadian phase exhibited higher levels of PAI-1. Age, BMI, and RAPA score were also significant predictors of PAI-1.

Up-mesor and PAI-1. Results of the regression using CAR-Upmesor to predict PAI-1 are presented in Table 17. There were significant main effects for CAR-Upmesor (β = 4.997, $t(142) = 2.223$, $p = .028$), caregiver age (β = -0.927, $t(142) = -2.634$, $p = .009$), and caregiver BMI (β = 1.439, $t(142) = 2.848$, $p = .005$). The was no significant main effect of caregiver physical activity as assessed by the RAPA, but inclusion of this variable did increase overall model fit. Since up mesor represents the time of day when activity shifts from 'low activity' to 'high activity', these results indicate that caregivers with a later circadian clock appear to exhibit increased PAI-1 levels. Additionally, caregivers who have increased BMI exhibit higher levels of PAI-1 while older caregivers show lower levels of PAI-1 at baseline. Other potential covariates of sex, years caregiving, scores, RMBC scores, and CDR total score were explored but did not result in improved model fit.

These results suggest that when adjusting for relevant covariates, up mesor is significantly associated with PAI-1 at baseline; caregivers with later transitions from low to high activity exhibited higher levels of PAI-1. Consistent with the previous analysis; age, BMI, and RAPA score were also significant predictors of PAI-1.

CAR-R^2 and IMT of the Common Carotid Artery. Results of the regression using CAR-R^2 to predict intima-media thickness of the common carotid artery are presented in Table 18. The main effect of CAR-R^2 was not statistically significant, but inclusion of this variable in the model did increase overall model fit. Caregiver age (β = 0.009, $t(142) = 3.342$, $p = .001$) and

RMBC Reaction scores ($\beta = 0.005$, $t(142) = 2.245$, $p = .026$) were both significant predictors of IMT-CCA such that caregivers who are older or report more severe reactions to care recipient problem behaviors exhibit thicker IMT of the common carotid artery at baseline. Potential covariates of sex, years caregiving, RAPA scores, RMBC Frequency score, and CDR total score were explored but did not result in improved model fit.

Due to the noted inequivalence of the means and variances of bot CAR-R^2 and IMT of the common carotid artery across the two studies, regressions were also fitted for each study individually. In study 1, none of the variables that were found to be predictors of IMT of the common carotid artery were significant in this reduced sample. In study 2, only age remained as a significant predictor of IMT of the common carotid artery ($\beta = 0.010$, $t(85) = 3.779$, $p < .001$).

These results suggest that when adjusting for relevant covariates, robustness of the circadian activity rhythm is not significantly associated with IMT of the common carotid artery at baseline. Caregiver age and the amount of distress they report in response to care recipient problem behaviors were significant predictors of IMT of the common carotid artery. Caregivers who are older or report more severe reactions to care recipient problem behaviors exhibit thicker IMT of the common carotid artery at baseline.

3.2 Aim 2: Longitudinal Associations between Sleep Variables and Markers of CVD Risk

The goal of aim 2 was to investigate the longitudinal associations between subjective, objective, and circadian sleep measures and markers of CVD risk and vascular pathology.

Longitudinal Sample Characteristics

Sample characteristics for study 1 can be found in Tables 19 (caregivers) and 20 (non-caregivers). Due to the study's rolling recruitment strategy, many participants do not have data for all 5 annual visits. The final sample includes 126 caregivers and 60 non-caregivers who all

had a baseline visit. These numbers gradually decrease; 93 caregivers and 55 non-caregivers have data for year 2, 64 caregivers and 49 non-caregivers have data for year 3, 38 caregivers and 39 non-caregivers have data for year 4, and 7 caregivers and 12 non-caregivers have data for year 5. Also, within each year assessment, data may be missing for various reasons (e.g., participants refused certain assessments, changes in study procedures). Insufficient circadian activity rhythm data were available from year 2 on, and thus these data are excluded from Tables 18 and 19. The combined sample of 186 participants includes 57 men (30.6%) and 129 women, mostly white (92.5%).

To assess for baseline differences between caregivers and non-caregivers, independent samples t-tests were conducted for each variable of interest grouped by caregiver status to examine significant differences in means and Levene's test for equality of variances. Levene's test revealed that the following variables have significantly different variances between caregivers and non-caregivers: CDR total score ($F_{1, 183} = 90.195$, $p < .001$), RMBC Frequency score ($F_{1, 184} = 24.941$, $p < .001$), RMBC Reaction score ($F_{1, 181} = 49.742$, $p < .001$), CES-D score ($F_{1, 183} = 18.145$, $p < .001$), PSQI score ($F_{1, 184} = 7.868$, $p = .006$), actigraphy total sleep time ($F_{1, 173} = 4.722$, $p = .031$), interleukin-6 ($F_{1, 171} = 4.412$, $p = .037$), epinephrine ($F_{1, 173} = 6.1187$, $p = .014$), norepinephrine ($F_{1, 173} = 4.828$, $p = .029$), and intima-media thickness of the common carotid artery ($F_{1, 172} = 5.509$, $p = .020$). Independent samples t-tests found significant mean differences in several variables. Caregivers had significantly higher mean CDR score ($t(177.773) = -23.166$, $p < .001$), RMBC Frequency and Reaction scores ($t(183.770) = -20.2219$, $p < .001$; $t(164.748) = -9.984$, $p < .001$), negative affect ($t(184) = -4.738$, $p < .001$), PSQI scores indicating greater sleep problems ($t(155.295) = -4.545$, $p < .001$), longer actigraphy total sleep time ($t(132.780) = -2.350$, $p = .020$), and higher epinephrine levels ($t(165.435) = -2.555$, $p =$

.012). Non-caregivers had significantly higher mean positive affect ($t(184) = 4.363$, $p < .001$) and physical activity as assessed by the RAPA ($t(184) = 2.304$, $p = .022$).

Multilevel Models of Longitudinal Relationships

Multilevel models were constructed to investigate potential longitudinal associations between each sleep predictor and each CVD risk/vascular outcome variable and potential effects of caregiver status on these associations. Models were constructed systematically including intercept-only model, random-coefficient regression model, and intercepts- and slopes-as-outcomes model. Model fit indices of AIC, BIC, and log likelihood were compared at each step to determine the best model for the included variables. Covariates were added to models revealing significant associations to test whether the observed associations remained significant. These analyses yielded five significant associations out of the thirty-nine predictor/outcome pairs explored.

PSQI Score and Flow-mediated Dilation. Results of the final multilevel models examining the relationship between PSQI scores and FMD can be found in Table 21. Initial intercept-only model revealed that the average FMD for the sample across time points was 10.438, $t(1,226) = 40.07$, $p < .001$. A random-coefficient model including only time as a level 1 predictor showed that there was a statistically significant decrease in FMD over time ($\gamma_{10} = -0.732$, $t(2, 225) = -4.113$, $p < .001$). Testing a variety of intercepts and slopes as outcomes models revealed that PSQI score was not a predictor of the expected value of the intercept of FMD. There was a statistically significant effect of PSQI scores on the relationship between time and FMD ($\gamma_{11} = 0.179$, $t(4, 223) = 2.115$, $p = 0.0355$), and this effect was different for caregivers and non-caregivers ($\gamma_{12} = -0.299$, $t(4, 223) = -2.639$, $p = 0.0089$).

Including RMBC Reaction score improved overall model fit but did not have a significant impact on the relationship between time and FMD. The interaction effect of PSQI score and caregiver status remained significant when including this covariate, however the main effect of PSQI score predicting the slope did not. For caregivers, higher average PSQI score across all available time points was associated with reductions in FMD over time.

PSQI Score and Baroreflex Sensitivity. Results of the final multilevel models examining the relationship between PSQI scores and BRS can be found in Table 22. Initial intercept-only model revealed that the average BRS for the sample across time points was 9.180, $t(1,155) = 15.575$, $p < .001$. A random-coefficient model including only time as a level 1 predictor showed that there was not a significant linear association of BRS across time ($\gamma_{10} = -0.624$, $t(2, 149) = 1.347$, $p = 0.1799$). Testing a variety of intercepts and slopes as outcomes models revealed that PSQI score was not a predictor of the expected value of the intercept of BRS. There was a statistically significant effect of PSQI scores on the relationship between time and BRS ($\gamma_{11} = -0.271$, $t(3, 148) = -1.997$, $p = 0.0476$). This effect did not differ between caregivers and non-caregivers.

Including covariates in the analysis revealed that average physical activity ($\gamma_{01} = 1.024$, $t(6, 153) = 3.353$, $p = 0.0010$) across all time points is significantly associated with the expected value of BRS at baseline. Age ($\gamma_{12} = 0.181$, $t(6, 146) = 3.361$, $p = 0.0010$) and sex ($\gamma_{13} = -2.121$, $t(6, 146) = -2.603$, $p = 0.0102$) had significant effects on the relationship between time and BRS. In this covariate adjusted model, the relationship between time and BRS was significant ($\gamma_{10} = 2.015$, $t(6, 146) = 2.402$, $p = 0.0175$), but the effect of PSQI scores on BRS over time was not ($\gamma_{11} = -0.202$, $t(6, 146) = -1.613$, $p = 0.1088$). These results indicate that for all male participants, there is an increase in BRS over time (this effect was not present for female participants).

Individuals with higher levels of physical activity have better BRS at baseline. Older participants had slightly better improvements in BRS over time. With regards to PSQI scores, the results indicate a trend toward higher subjective sleep impairment being associated with worse BRS over time; however, this association was not statistically significant.

Actigraphy Percent Sleep and Baroreflex Sensitivity. Results of the final multilevel models examining the relationship between actigraphy percent sleep and BRS can be found in Table 23. Initial intercept-only model revealed that the average BRS for the sample across time points was 9.180, $t(1,155) = 15.575$, $p < .001$. A random-coefficient model including only time as a level 1 predictor showed that there was not a significant linear association of BRS across time ($\gamma_{10} = -0.624$, $t(2, 149) = 1.347$, $p = 0.1799$). Testing a variety of intercepts and slopes as outcomes models revealed that percent sleep was not a predictor of the expected value of the intercept of BRS. Including the effect of percent sleep on the relationship between time and BRS improved model fit but was not statistically significant ($\gamma_{11} = -0.151$, $t(4, 144) = -1.179$, $p = 0.2404$). However, there appeared to be a difference in this effect for caregivers and non-caregivers ($\gamma_{11} = 0.346$, $t(4, 144) = 2.025$, $p = 0.0447$). Caregivers with higher percent sleep appeared to experience better BRS over time compared to non-caregivers.

Including covariates in this model rendered all associations between percent sleep and BRS non-significant. Average physical activity ($\gamma_{01} = 1.012$, $t(6, 150) = 2.582$, $p = 0.0011$) across all time points is significantly associated with the expected value of BRS at baseline. Age ($\gamma_{12} = 0.163$, $t(6, 143) = 3.002$, $p = 0.0032$) and sex ($\gamma_{13} = -2.418$, $t(6, 143) = -2.896$, $p = 0.0044$) had significant effects on the relationship between time and BRS. In this covariate adjusted model, the relationship between time and BRS was significant ($\gamma_{10} = 2.220$, $t(6, 143) = 2.582$, $p = 0.0108$). These results indicate that for all male participants, there is an increase in BRS over

time (this effect was not present for female participants). Individuals with higher levels of physical activity have better BRS at baseline. Older participants had slightly better improvements in BRS over time. With regards to percent sleep, the results indicate a trend toward higher objective percent sleep being associated with improved BRS over time; however, this association was not statistically significant.

Actigraphy Percent Sleep and Heart Rate. Results of the final multilevel models examining the relationship between actigraphy percent sleep and heart rate can be found in Table 24. The initial intercept-only model revealed that the average heart rate for the sample across time points was 64.620, $t(1,350) = 100.687$, $p < .001$. A random-coefficient model including only time as a level 1 predictor showed that there was a statistically significant decrease in heart rate over time ($\gamma_{10} = -0.768$, $t(2, 348) = -3.137$, $p = .0018$). In the final model (i.e., model with optimum model fit indices) percent sleep was a significant predictor of both the expected value of the intercept ($\gamma_{01} = -0.379$, $t(4, 174) = -2.702$, $p = 0.0076$) and slope of heart rate over time ($\gamma_{11} = 0.183$, $t(4, 344) = 2.686$, $p = 0.0076$). For every percentage point increase in average percent sleep, the intercept of heart rate (i.e., the predicted value of heart rate at baseline) decreased by 0.379 and the slope of heart rate over time increased by 0.183.

Including the covariates of RAPA score, RMBC Reaction score, and sex as predictors of the expected value of the intercept of heart rate improved model fit, however none of these associations were statistically significant. The effect of sex on the relationship between heart rate and time was statistically significant ($\gamma_{12} = 1.392$, $t(8, 343) = 2.231$, $p = 0.0263$). For men, the slope of heart rate over time was 1.392 greater than for women. The effects of percent sleep on the expected value of the slope and the relationship between heart rate and time remained statistically significant when covariates were included in the model.

Actigraphy Percent Sleep and Norepinephrine. Results of the final multilevel models examining the relationship between actigraphy percent sleep and norepinephrine can be found in Table 25. The initial intercept-only model revealed that the average norepinephrine level for the sample across time points was 530.622, $t(1,294) = 45.731$, $p < .001$. A random-coefficient model including only time as a level 1 predictor showed that there was not a significant linear association of norepinephrine across time ($\gamma_{10} = -11.798$, $t(2, 293) = -1.014$, $p = 0.3114$). Testing a variety of intercepts and slopes as outcomes models revealed that percent sleep was a significant predictor of the expected value of the intercept of norepinephrine over time ($\gamma_{10} = -11.798$, $t(2, 293) = -1.014$, $p = 0.3114$) but not the slope. For every percentage point increase in average percent sleep, levels of norepinephrine at baseline decreased by 11.798.

The inclusion of RMBC Reaction score as a predictor of the intercept of norepinephrine and sex as a predictor of the slope of norepinephrine over time improved model fit, however neither of these effects were statistically significant. The effect of percent sleep on the expected value of the intercept of norepinephrine remained significant when covariates were included in the model.

3.3 Aim 3: Effects of Behavioral Activation Intervention on Sleep and CAR Variables

The goal of aim 3 was to explore the ability of a brief behavioral activation intervention to improve subjective, objective, and circadian sleep variables compared with an enhanced treatment as usual condition.

Intervention Sample Characteristics

Sample characteristics for study 2 can be found in Table 26. This study sample included 150 caregivers were randomly assigned to either the behavioral activation or information support conditions. The sample included 34 men (22.7%) and 116 women, overwhelmingly white (88.7%). Caregivers ranged in age from 56.4 to 93.4 years old (M = 73.49 years, SD = 7.99). Participants had been caregiving for an average of 4.63 years at the time they entered the study (SD = 3.23). Participants in the behavioral activation condition had significantly lower average actigraphy total sleep time ($t(108) = 2.131$, $p = .035$) and significantly higher average CAR – Slope ($t(118) = -2.225$, $p = .028$) and Width Ratio ($t(118) = -2.236$, $p = .027$) compared to participants in the information support condition.

Multilevel Models Testing the Effect of Treatment Condition on Sleep Parameters

Multilevel models were constructed to investigate potential effects of treatment condition (i.e., information support or behavioral activation/PEP). Models were constructed systematically including intercept-only model, random-coefficient regression model, and intercepts- and slopes-as-outcomes model. Random-coefficient regression models including only time as a level 1 predictor showed that there were significant linear relationships across time for only two sleep variables: ISI scores and CAR-$F_{improve}$. However, intercepts- and slopes-as-outcomes models revealed that there was no significant effect of treatment condition on the slopes of these linear relationships.

Pre-Post ANOVA Analyses

Given that many of the sleep outcomes did not show linear relationships across time from pre-treatment to 12-month follow-up, ANOVAs were conducted to investigate whether treatment condition had any significant impact on change in sleep parameters from pre- to post-treatment.

Results for these ANOVAs can be found in Table 27. There were no significant differences in pre-to-post changes in any of the observed sleep parameters associated with treatment condition.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Brent Mausbach, Ph.D., Sonia Ancoli-Israel, Ph.D., Igor Grant, M.D., Jonathan Helm, Ph.D., and Vanessa Malcarne, Ph.D. The dissertation author was the primary investigator and author of this material.

Chapter 4: Discussion

Despite increased use of evidence-based medical therapies for secondary prevention and lifestyle and environmental changes in the population leading to decreased risk factors, cardiovascular disease remains the leading cause of death both in the United States and globally. Caregivers experience greater cardiovascular morbidity compared to their non-caregiving counterparts. A more thorough understanding of the unique stressors experienced by caregivers and their relationship to intermediary processes (e.g., dysregulation of the HPA axis, abnormal modulation of the autonomic nervous system, increased sympathetic nervous system activity, increased systemic inflammation, and increased atherogenesis) could elucidate how CVD develops over time and help to identify additional risk factors as targets for preventative treatments.

Research over the past 20 years has implicated sleep, particularly insomnia, as a possible risk factor for CVD. However, much of this research is inconsistent due to variations in the way insomnia is defined. Furthermore, little attention has been paid to the possible associations of dysregulated circadian rhythms and the development of CVD. This dissertation aimed to analyze the associations between subjective sleep quality, objective sleep parameters, and circadian activity rhythms with various markers of CVD risk and vascular pathology in a sample of elderly Alzheimer's caregivers. The three aims of this dissertation were 1) to examine cross-sectional associations between subjective and objective sleep measures, circadian activity rhythm (CAR) and markers of CVD risk in Alzheimer's caregivers, 2) to observe longitudinal associations between subjective and objective sleep measures and markers of CVD risk in Alzheimer's caregivers, and 3) to test the ability of a brief BA intervention to improve subjective and objective sleep measures and CAR in Alzheimer's caregivers.

4.1 Aim 1: Cross-sectional Associations between Sleep Variables and Markers of CVD Risk

The goal of aim 1 was to assess the cross-sectional associations between subjective/objective sleep and CAR variables with markers of CVD risk and vascular pathology.

Correlations between Sleep Variables and Markers of CVD Risk

Using the combined data from both studies, Pearson product-moment correlations identified 15 significant associations to be further explored with multiple linear regression. With regards to subjective sleep variables, the only significant association was between ISI score and levels of D-Dimer; caregivers reporting greater insomnia severity had higher levels of D-Dimer. Objective sleep measures (i.e., actigraphy total sleep time and percent sleep) exhibited no significant associations with any of the observed CVD markers. There were numerous associations between various circadian activity rhythm variables and CVD markers, including baroreflex sensitivity, TNF-α, von Willebrand factor, PAI-1, and intima-media thickness of the common carotid artery.

The results showed the greatest evidence for associations between circadian activity rhythm variables and BRS. The correlations suggest that caregivers with greater amplitude (i.e., maximum minus minimum activity values obtained from actigraphy) exhibited greater BRS, but individuals with a higher minimum activity value had decreased BRS at baseline. Additionally, caregivers with an earlier up-mesor (i.e., time of day that activity shifts from below the mesor to above the mesor) displayed greater BRS. Caregivers with a higher width ratio, or amount of time where activity was above the mesor, showed higher BRS. Lastly, caregivers with greater CAR-R^2, CAR-F statistic, and CAR-$F_{improve}$ (all measures of the strength of the circadian rhythm) showed significantly greater BRS at baseline. These results suggest that individuals with

consistent circadian rhythms, with higher levels of activity, and earlier start times for their activity would experience the best BRS in this sample.

Circadian activity rhythm variables were correlated with various CVD risk markers and indicators of vascular pathology. Greater slope (i.e., an indicator of how quickly activity changes from minimum to maximum) was associated with higher levels of TNF-α at baseline. This suggests that caregivers with more rapid transitions between low and high activity have higher circulating levels of the inflammatory cytokine. Amplitude, mesor, and CAR-R^2 were all negatively correlated with von Willebrand factor. Caregivers with greater difference between maximum and minimum activity, higher midpoint activity level, and more consistent circadian rhythm exhibited lower levels of this marker of blood coagulability. Later acrophase and up-mesor were both positively correlated with PAI-1; caregivers with later times of peak activity and later times of transition from low to high activity had higher levels of PAI-1, and therefore at risk for higher coagulability. Lastly, CAR-R^2 was negatively associated with intima-media thickness of the carotid artery. Caregivers with weaker (i.e., less consistent) circadian activity rhythms had thicker IMT, suggesting that intermediary processes were already manifesting vascular pathology.

Multiple Linear Regressions of Identified Associations

These associations were then further examined with multiple linear regression to determine if they remained significant when controlling for relevant covariates. The pool of covariates that were tested were determined a priori from previous research showing associations between various demographic variables and indicators of caregiver stress with the CVD risk marker variables of interest. The covariates considered in the cross-sectional associations were

age, sex, BMI, RMBC (both frequency and reaction scales), CDR (total score only), ZBI, years caregiving, and physical activity assessed with the RAPA.

For the analyses of aim 1, the samples from both studies were combined to increase the power of the analyses. It was assumed that since the inclusion/exclusion criteria for both studies were nearly identical that the samples should also be identical (i.e., equivalent with. The significant differences between the samples on many of the variables of interest were not anticipated. For analyses that included variables that were significantly different between the two samples, additional regression models were run for each sample independently to determine if the associations differed across samples.

As expected, many of these variables had strong associations with the CVD risk outcome variables and increased model fit indices of the multiple linear regression analyses. BMI was a strong predictor of BRS, D-Dimer, TNF-α, vWF, and PAI-1. RAPA scores were strongly associated with D-Dimer, BRS, and PAI-1. RMBC-Frequency scores, a measure of the frequency of care recipient problem behaviors reported by caregivers, was strongly associated with D-Dimer, BRS, and TNF-α. RMBC-Reaction scores, a measure of how distressing caregivers rated care recipient problem behaviors, was a strong predictor of TNF-α, PAI-1, and IMT of the common carotid artery. Age was associated with TNF-α, vWF, PAI-1, and IMT of the common carotid artery. On many occasions, inclusion of these covariates accounted for significant amounts of variance in the data and rendered the association between the sleep/circadian activity rhythm and CVD variables of interest non-significant; of the 15 significant associations identified using Pearson product-moment correlations, 8 remained statistically significant in the covariate adjusted linear regression models. Up-mesor and CAR-*F* statistic both remained significant predictors of BRS in their respective covariate adjusted

models. CAR-R^2 and CAR-$F_{improve}$ also remained significant predictors of BRS, but only in the study 2 sample (i.e., the intervention study). Slope remained a significant predictor of TNF-α, but only in the study 1 sample (i.e., the longitudinal study). Mesor remained a significant predictor of vWF in the combined study sample and in the study 1 sample, but not in the study 2 sample. Acrophase and up-mesor both remained significant predictors of PAI-1.

These results provide mixed support for the initial hypotheses. With only one significant correlation identified (ISI scores and TNF-α), the results showed minimal support for the association between subjective sleep quality and markers of CVD risk and vascular pathology. Contrary to the hypotheses for aim 1, there was no evidence to support associations between objective sleep variables (actigraphy total sleep time and percent sleep) and markers of CVD risk. However, there was modest support for an association between circadian activity rhythm variables and various markers of CVD risk and vascular pathology. Furthermore, many of these circadian activity rhythm variables showed independent associations with CVD risk variables when controlling for caregiver burden. This suggests that circadian activity rhythm misalignment could pose an independent risk factor for the development of CVD in addition to caregiver stress.

4.2 Aim 2: Longitudinal Associations between Sleep Variables and Markers of CVD Risk

The goal of aim 2 was to assess the associations between subjective and objective measures of sleep and markers of CVD risk over time using multilevel models. These analyses allowed for the examination of the independent effects of predictor variables on both the intercept and slope of the regression equations. Interaction terms were included to determine if the effects of the sleep variables of interest on the intercepts and slopes differed by caregiver status. The intercepts- and slopes-as-outcomes models revealed five significant associations out of a possible thirty-nine predictor/outcome pairs, providing sparse evidence for the proposed

hypotheses. An interaction effect of caregiver status was observed in two of the five significant relationships, indicating that most of the associations between sleep variables and markers of CVD risk did not differ between caregivers and non-caregivers. Some of these significant associations were not significant once relevant covariates were included in the model. Furthermore, some of the significant associations were in the opposite direction predicted by our hypotheses.

Longitudinal Analyses for Subjective Sleep Variables

FMD demonstrated a decrease over time as evidenced by the significant negative effect of time in the intercepts and means as outcomes model. PSQI score was a significant predictor of the slope of FMD; in caregivers with higher PSQI scores, the relationship between time and FMD was more positive. In other words, increased sleep disturbance was associated with less impaired FMD over time. Although this result appears to directly contradict our original hypothesis, there was also a significant interaction of PSQI scores and caregiver status. This indicates that the slope of FMD over time was significantly lower for caregivers compared to non-caregivers. Taken together, these results suggest that all individuals experience a decrease in FMD over time, however this decrease is most pronounced in caregivers. The interaction effect of PSQI and caregiver status remained statistically significant when controlling for relevant covariates. It was anticipated that impaired sleep would be associated with decreased FMD over time. Therefore, these results provide support for our hypotheses.

An intercepts- and means-as-outcomes model revealed that PSQI score was a significant predictor of the slope of BRS such that individuals with greater sleep disturbance experienced more impaired BRS over time. In the covariate adjusted model, PSQI score was no longer a significant predictor of the slope. RAPA was a significant predictor of the intercept while time,

age, and sex were all significant predictors of the slope. Together, these results suggest that men experience improved BRS over time while women's BRS is relatively stable. Higher levels of physical activity were associated with better BRS at baseline. Older participants experienced slightly better improvements in BRS over time. Though the coefficient for PSQI scores was in the anticipated direction (i.e., more disturbed sleep was associated with worse BRS over time), this relationship was not statistically significant.

Longitudinal Analyses for Objective Sleep Variables

The intercepts and slopes as outcome model examining the effect of actigraphy sleep efficiency on BRS showed a significant interaction effect of percent sleep and caregiver status predicting the slope of BRS over time. This suggests that caregivers with higher percent sleep experience greater improvements in BRS over time. However, in the covariate adjusted model the effect of percent sleep on BRS was insignificant. There was a increase in BRS over time. RAPA was a significant predictor of the expected value of the intercept such that individuals with higher levels of physical activity had better BRS at baseline. Additionally, age and sex were significant predictors of the expected value of the slope of BRS over time. Older individuals appeared to experience greater improvements in BRS over time, but BRS over time appeared relatively stable for women. Given that impaired BRS has been shown to be associated with total cardiac mortality (La Rovere, Pikka, & Raczak, 2008), it was anticipated that percent sleep would be positively associated with BRS. Therefore, this non-significant result does not support our initial hypotheses.

In the analyses examining the association between percent sleep and heart rate, the intercepts and slopes as outcomes model revealed percent sleep was a significant predictor of the expected value of the intercept and slope, and time was a significant predictor of the slope. These

results suggest that individuals with higher percent sleep have lower heart rates at baseline and heart rate exhibits a decrease over time. However, individuals with increased percent sleep experience less negative slopes of heart rate over time. These effects remained significant in the covariate adjusted model. Sex was also a significant predictor of the expected value of the slope such that women experienced less negative slopes in heart rate over time. It was anticipated that percent sleep would be negatively associated with heart rate as research has clearly demonstrated that individuals with higher resting heart rate are at higher risk of CVD, CHD, and total mortality (Cooney et al., 2010). However, a recent study has also shown that low baseline heart rate (<65 bpm) was associated with increased risk of CVD (HR, 1.19; 95% CI, 1.07–1.32) when compared to a moderate heart rate group (65 to 80 bpm). Furthermore, compared with stable heart rate in the moderate heart rate group, a decrease in heart rate in the low heart rate group was also associated with increased risk of CVD (HR, 2.48; 95% CI, 1.27–4.82; Tian et al., 2019). Therefore, the observed results could support our initial hypothesis: that impaired percent sleep would be associated with poor CVD outcomes.

Percent sleep also showed a significant association with norepinephrine. In the intercepts and slopes as outcomes model, percent sleep was a significant predictor of the expected value of the intercept; individuals with higher percent sleep demonstrated significantly higher levels of norepinephrine at baseline. There was no significant effect of time, suggesting that norepinephrine levels do not follow a linear trajectory longitudinally. The effect of percent sleep on the expected value of the intercept remained significant in the covariate adjusted model. Given that norepinephrine is an indicator of SAM arousal, these results contradict our hypotheses. These results are also inconsistent with previous research showing that increased

wake after sleep onset is positively associated with increased norepinephrine levels (Mausbach et al., 2006).

The results for aim 2 provided scant support for the original hypotheses as few significant results were identified and many results directly contradicted the hypothesized relationships between sleep disturbance and markers of CVD risk and vascular pathology. Only the relationship between PSQI scores and FMD occurred as predicted, with greater sleep disturbance being associated with impaired FMD, a known risk factor for CVD. The results that show improvements in markers of CVD risk over time or with greater sleep disturbance are difficult to explain. It is possible that the recruitment strategy employed by the study had an adverse effect on the multilevel analyses. The study relied on rolling recruitment, meaning that participants were recruited continuously over the 5-year study period. However, this also meant that participants recruited in later years were eligible for fewer assessments. Therefore, even though the final sample includes baseline data for 126 caregivers and 60 non-caregivers, these numbers gradually decrease each year. Data was available for 93 caregivers and 55 non-caregivers for year 2, 64 caregivers and 49 non-caregivers for year 3, 38 caregivers and 39 non-caregivers for year 4, and 7 caregivers and 12 non-caregivers for year 5. Since multilevel modeling is sensitive to participants with more complete data, it is possible that the results were significantly skewed by a small number of participants.

4.3 Aim 3: Effects of Behavioral Activation Intervention on Sleep and CAR Variables

The final aim of this dissertation was to observe the potential for a Behavioral Activation intervention to improve subjective/objective sleep and circadian activity rhythm variables. Using data from study 2, multilevel models were constructed to assess the effect of treatment condition (behavioral activation vs. information support) on each sleep outcome of interest over time. A

linear relationship over time was observed for two of the fifteen variables of interest: ISI scores and CAR-$F_{improve}$. Multilevel models showed revealed that treatment condition was not a significant predictor of the expected value of the slope for any of the variables of interest.

Given that most of the sleep variables did not show linear relationships over time, a key assumption of multilevel models, post hoc pre-post ANOVAs were conducted to determine if treatment condition was associated with significant differences in change in sleep and circadian activity variables from pre- to post-treatment. There were no significant differences in pre-to-post changes in any of the observed sleep parameters associated with treatment condition. Therefore, the results provide no support for the initial hypotheses.

4.4 Summary and Context within Existing Literature

This dissertation endeavored to clarify the relationships among various dimensions of sleep (subjective sleep quality, objective sleep parameters, and circadian activity rhythm variables) with various cardiovascular risk markers, including markers for inflammation, procoagulant shift, and evidence of atherosclerosis and vascular pathology. The results show some associations cross-sectionally between CAR variables and various markers of vascular pathology. Longitudinal analyses revealed significant relationships between objective sleep parameters, particularly percent sleep, with resting heart rate and norepinephrine. Lastly, the Behavioral Activation intervention was not more effective than the Information Support condition at improving any markers of CG sleep quality, quantity, or CAR.

The association between insomnia and increased risk of CVD has been established for some time (Schwartz, 1999; Sofi et al., 2014). However, the association between circadian rhythms and CVD is an area of ongoing investigation. Analyses from the Study of Osteoporotic Fractures showed that older women with weaker CAR had significantly increased risk of all-

cause, atherosclerotic, stroke, and "other" mortality independent of relative confounders. The authors opined that either activity rhythms posed an additional risk factor for mortality in older women or circadian activity rhythms may act as biomarkers of advanced physiological aging. Therefore, CAR may provide markers for individuals with increased risk of atherosclerotic, stroke, or cancer death not measured by conventional markers (Tranah et al., 2010). The observed associations between CAR and various markers of vascular pathology support the latter explanation. More recent research has demonstrated that individuals in laboratory induced chronic circadian misalignment exhibited lower levels of 24-hour cortisol and increased levels of TNF-α, CRP, and IL-10 (Wright Jr. et al., 2015). The current study expands on this research by examining the association between naturalistic CAR patterns with inflammatory biomarkers, cytokine balance, and other markers of vascular pathology. However, the current analyses provide more evidence for an association between CAR and impaired BRS, which may be related to the development of hypertension (Parmer, Cervenka, & Stone, 1992). These results also suggest that CAR may act as a marker of increased CVD risk in Alzheimer's CG similar to what was observed in the Study of Osteoporotic Fractures.

The present study found few longitudinal associations between subjective sleep quality, objective sleep variables, and markers of vascular risk and pathology. Furthermore, insufficient CAR data were available to examine potential longitudinal relationships, which may have provided greater evidence for a causal association of weakened activity rhythms and markers of vascular pathology. The brief Behavioral Activation intervention was also ineffective at improving sleep parameters, suggesting that other interventions may be necessary in order to improve sleep outcomes for caregivers.

4.5 Study Limitations and Future Directions

The results of this dissertation should be interpreted in the context of the study limitations. For aim 1, samples from two studies were combined to increase the power of the proposed analyses. The inclusion/exclusion criteria of the studies were nearly identical, with study 2 including an added criterion that participants must screen positive for depressive symptoms during a brief phone screen as assessed by the PHQ-2. It was assumed that the two study samples would be roughly equivalent with regards to the variables of interest and could be combined without issue. Independent samples t-tests and Levene's tests revealed significant differences in several variables based on study. These differences raise the question of whether there was something fundamentally different. The sample of study 2 does exhibit significantly higher scores on the CES-D and higher levels of negative affect, which might be expected due to the additional inclusion criteria. It is less clear why there would be significant differences between studies in intima-media thickness of all measured sites (i.e., common carotid artery, bifurcation, and internal carotid artery). The ultrasound interrogation angles differed slightly between the two studies (Study 1 - Right: 180° and 120°, Left: 180° and 240°; Study 2 - Right: 150° and 90°, Left: 210° and 270°); however, this does not satisfactorily explain the approximately 20% difference in IMT observed between the two studies. It is possible that some other assessment error contributed to these wide variations. There were also significant differences in some of our CVD risk biomarkers (D-Dimer and TNF-α). Given that these biomarker data were obtained via the same assay across studies, the differences seem unlikely to be due to assessment error. It is possible that variations in blood sample storage time and/or procedure prior to assay resulted in diminished recovery of biomarkers from the samples if sample collection procedures changed between the two studies. The samples also exhibited

significant differences in CDR and RMBC-Reaction scores occurring in potentially contradictory directions. Participants in study 1 reported higher average CDR scores, meaning that on average they were caring for care recipients with greater impairment. However, participants in study 2 reported significantly higher reaction to care recipient problem behaviors, despite participants in both studies reporting roughly equivalent frequency of problem behaviors. It is possible that the increased RMBC-Reaction scores were related to the increased symptoms of depression reported by participants in study 2. Lastly, the samples showed significant differences in CAR-mesor and CAR-R^2. Circadian activity rhythm variables were derived using the same R code and technician for both studies. It is unclear why the samples would differ regarding these two variables and no other circadian activity rhythm variables.

Despite the noted differences between the two study samples, the data were analyzed as a combined sample as originally planned. This was done to maximize the power. Subsequent analyses were conducted by study sample to observe if there were differences between the two studies. However, it could be argued that combining the samples for these analyses was inappropriate due to their non-equivalence.

This study included numerous planned analyses for which no corrections of multiple comparisons were performed. Given the sheer number of planned comparisons, it is possible that some results were statistically significant due to chance and not reflective of a true effect. As this was essentially and exploratory study, we decided not to perform any such correction. Future studies should use the results of this dissertation as a guide to focus on specific analyses and confirm these findings using the appropriate corrections.

There were significant sources of data loss, which negatively impacted analyses in a variety of ways. The rolling recruitment strategy utilized by both studies meant that participants

recruited later in the study were eligible for fewer assessments. Combined with natural attrition and caregiver status changes due to care recipient placement in a care facility or death, only 7 out of 126 caregivers and 12 out of 60 non-caregivers had data for year 5 of study 1. Multilevel modeling tends to give more weight to participants with more waves of data, so this may have influenced the analyses of aim 2. There was also a disproportionate loss of circadian activity rhythm data due to administrative error, significantly impacting the power of analyses in aim 1 and providing insufficient data to analyze longitudinal patterns in aim 2.

The original data analysis plan for aim 3 was to use multilevel models to examine whether treatment condition influenced the slope of sleep and circadian activity rhythm variables over time. Unfortunately, many of these variables did not show a linear relationship from pre-treatment to 12-month follow-up. A post hoc analysis was conducted comparing pre-post change in sleep variables by study condition using ANOVAs, however this analysis also failed to find significant results. There are a few reasons why the BA intervention showed no significant effects. First, BA is a treatment that has been shown to be effective for treating depression, not sleep disturbance. It was thought that BA may have an effect on sleep through a mediating effect of reduced depressive symptoms, or that increased activity could encourage more consistent circadian activity rhythms (i.e., increased activity and scheduling would lead to more robust activity schedules). Furthermore, it should be noted that the tested intervention was a brief version of a validated intervention that was adapted specifically for caregivers. It is possible that the treatment dose simply was not large enough to observe the hypothesized effect. And lastly, the IS condition can be considered an enhanced form of treatment as usual for caregivers. Given that caregivers had the ability to tailor the IS condition to meet their needs, it is possible that the IS condition was more effective than a regular control condition, which may explain why there

were no observed differences in effect between the IS and BA conditions. It should also be noted that the primary goal of the intervention study from which these data were taken was to observe the effect of treatment condition on reductions in CVD risk biomarkers. This effect was not observed. Instead, secondary analyses showed that caregivers whose spouse had severe functional impairment or who exhibited high levels of problem behaviors distress, had high positive and negative affect, or exhibited high mastery were more likely to experience reductions in certain biomarkers regardless of treatment condition (von Känel et al., 2020). Therefore, the results of aim 3 are consistent with the results of this study, showing no simple effect of treatment condition. Future analyses could investigate whether caregivers with higher levels of distress or other factors at baseline showed greater improvement in sleep variables with treatment.

Another significant limitation of this research is the lack of diversity in the study samples. Both study samples were overwhelmingly white women with low reports of sleep complaints and adequate total sleep time and percent sleep at baseline. The lack of diversity in the sample limits the generalizability of the results. Furthermore, the relatively low levels of sleep disturbance for both subjective and objective sleep measures may have introduced a ceiling effect to analyses. Future studies could examine these relationships in caregivers with significant reports of insomnia or potentially circadian rhythm disorders (e.g., delayed sleep phase or advanced sleep phase syndrome).

In addition to the future directions mentioned above, future studies should further explore the relationships between circadian activity rhythms and markers of vascular risk/pathology. Previous research has shown that reduced amplitude and greater minimum activity counts were associated with an increased risk of CVD in a cohort of older men (Paudel et al., 2010). To our

knowledge, this is the first study showing that various components of circadian activity rhythms are associated with several intermediary markers of CVD risk, including BRS, TNF-α, vWF, and PAI-1. Further research is needed to confirm these findings, clarify the mechanism by which circadian activity rhythms affect these intermediary CVD risk markers, and explore how circadian activity rhythms affect CVD risk longitudinally.

4.6 Conclusions

It has been long known that caregivers are at increased risk of CVD compared to their non-caregiving peers, and sleep has been implicated as a possible contributor to poor cardiovascular health. The present study provides new insights into the associations of sleep dimensions with multiple biomarkers of CVD risk in elderly caregivers. Although many of the initial hypotheses were not supported, the current study showed greater evidence for a cross-sectional association of markers of CVD risk with circadian activity rhythms than with measures of subjective sleep quality or objective sleep variables. These novel results reinforce the importance of examining multiple dimensions of sleep to fully appreciate the impact of sleep on health. Further research is needed to confirm these findings and further explore how sleep dimensions are associated with cardiovascular health over time, however these results highlight the particular importance of circadian activity rhythms in the development of CVD.

The results of this dissertation are being prepared for publication. Publications based on this dissertation will be co-authored by Brent Mausbach, Ph.D., Sonia Ancoli-Israel, Ph.D., Igor Grant, M.D., Jonathan Helm, Ph.D., and Vanessa Malcarne, Ph.D. The dissertation author was the primary investigator and author of this material.

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TABLES

Table 1. Baseline Study Characteristics

	Study 1 *n* = 126	Study 2 *n* = 169	Aggregated Sample *n* = 295
Patient Characteristics			
Gender			
Men	37 (29.4%)	38 (22.5%)	75 (25.4%)
Women	89 (70.6%)	131 (77.5%)	220 (74.6%)
Race/Ethnicity			
Black or African American	3 (2.4%)	8 (4.7%)	11 (3.7%)
American Indian or Alaskan Native	2 (1.6%)	2 (1.2%)	4 (1.3%)
Asian	0 (0.0%)	5 (2.9%)	5 (1.7%)
Native Hawaiian or Pacific Islander	1 (0.8%)	4 (2.3%)	5 (1.7%)
White	120 (95.2%)	147 (87.0%)	267 (89.6%)
Age, years	74.15 (7.94)	73.77 (8.02)	73.93 (7.98)
Years Caregiving	4.33 (3.39)	4.65 (3.43)	4.52 (3.41)
CDR Score*	1.64 (0.65)	1.37 (0.59)	1.49 (0.63)
RMBC – Frequency	34.67 (12.99)	36.59 (13.24)	35.75 (13.14)
RMBC – React*	14.08 (11.81)	33.01 (15.23)	24.69 (16.71)
CESD*	8.73 (5.80)	11.43 (5.24)	10.27 (5.64)
ZBI	n/a	33.66 (7.93)	33.66 (7.93)
PA	31.79 (7.43)	32.67 (7.18)	32.29 (7.29)
NA*	17.96 (6.03)	21.21 (6.91)	19.82 (6.73)
RAPA	3.42 (1.64)	3.28 (1.68)	3.34 (1.66)
BMI	26.49 (4.71)	27.50 (5.85)	26.99 (5.32)
Sleep Variables			
PSQI Score	6.69 (3.57)	7.35 (3.49)	7.07 (3.53)
Total ISI Score	n/a	7.95 (5.71)	7.95 (5.71)
Actigraphy Total Sleep Time, hours	7.30 (1.13)	7.35 (1.18)	7.33 (1.15)
Actigraphy Sleep Efficiency, %	87.31 (5.35)	87.04 (5.49)	87.18 (5.41)
CAR – Amplitude	1.79 (0.39)	1.69 (0.32)	1.71 (0.34)
CAR – Minimum	0.27 (0.20)	0.25 (0.18)	0.26 (0.19)
CAR – Mesor*	1.17 (0.20)	1.09 (0.16)	1.11 (0.18)
CAR – Slope	23.08 (22.43)	18.21 (27.57)	19.37 (26.45)
CAR – Acrophase	14.26 (1.20)	14.59 (1.14)	14.51 (1.16)
CAR – Up-Mesor	6.84 (1.26)	6.99 (1.23)	6.95 (1.23)
CAR – Down-Mesor	21.69 (1.53)	22.18 (1.48)	22.06 (1.50)
CAR – Width Ratio	0.62 (0.06)	0.63 (0.06)	0.63 (0.06)
CAR – R squared*	0.51 (0.14)	0.43 (0.17)	0.45 (0.13)
CAR – F statistic	2042.37 (2468.26)	2061.06 (1190.48)	2056.59 (1582.77)
CAR – F improve	684.54 (671.39)	746.85 (616.37)	731.95 (628.41)

Table 1. Baseline Study Characteristics Continued

	Study 1 *n* = 126	Study 2 *n* = 169	Aggregated Sample *n* = 295
Vascular Variables			
BRS, ms/mmHg	8.31 (7.47)	9.27 (5.25)	8.94 (6.11)
MAP*, mmHg	95.32 (9.62)	92.57 (11.23)	93.79 (10.62)
Resting Heart Rate, bpm	65.99 (10.00)	66.68 (10.41)	66.38 (10.22)
CRP, mg/L	3.70 (6.34)	2.95 (3.81)	3.28 (5.08)
IL6, pg/mL	1.51 (2.00)	1.13 (1.61)	1.30 (1.80)
TNF-α*, pg/mL	6.12 (2.70)	2.10 (0.77)	3.85 (2.73)
EPI, pg/mL	42.67 (42.95)	42.91 (58.11)	42.71 (45.19)
NE, pg/mL	510.21 (243.30)	463.39 (676.20)	503.48 (337.40)
PAI-1, ng/mL	36.71 (30.12)	32.38 (32.47)	34.29 (31.47)
D-Dimer*, ng/mL	768.16 (430.41)	508.13 (146.24)	623.70 (332.50)
vWF, mg/dL	176.64 (109.31)	154.81 (108.42)	164.51 (109.16)
FMD, % increase	11.00 (4.22)	n/a	11.00 (4.22)
IMT – CCA*, mm	0.80 (0.14)	1.08 (0.22)	0.93 (0.23)
IMT – BIF*, mm	0.87 (0.19)	1.20 (0.24)	1.04 (0.27)
IMT – INT*, mm	0.72 (0.17)	0.94 (0.24)	0.82 (0.23)

Note. * denotes significant differences in the mean of the variable between the two studies; CDR = Clinical Dementia Rating; RMBC = Revised Memory and Behavior Checklist; CESD = Center for Epidemiological Studies-Depression; ZBI = Zarit Burden Inventory; PA = positive affect; NA = negative affect; RAPA = Rapid Assessment of Physical Activity; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; ISI = Insomnia Severity Index; CAR = circadian activity rhythm; CRP = C-reactive protein; IL6 = Interleukin 6; TNF-α = Tumor Necrosis Factor alpha; EPI = epinephrine; NE = norepinephrine; PAI-1 = plasminogen activator inhibitor 1; vWF = von Willebrand factor; FMD = flow-mediated dilation; IMT = intima-media thickness; CCA = common carotid artery; BIF = bifurcation; INT = internal carotid artery.

Table 2. Statistical Tests for Equivalence of Means and Variances across Study Samples

	Levene's Test for Equality of Variances		*t*-tests for Equality of Means		
Variable	*F* statistic	*p* value	*t* statistic	df	*p* value
PSQI Score	0.140	.708	-1.594	293	.112
TST	0.060	.807	-0.355	230	.723
Sleep %	0.115	.735	0.373	230	.709
Amplitude	4.381	.038	1.564	54.786	.124
Minimum	0.036	.849	0.543	161	.084
Mesor	2.009	.149	2.270	161	.025
Slope	0.882	.349	1.002	161	.318
Acrophase	0.026	.873	-1.515	161	.132
Up Mesor	1.158	.238	-0.659	161	.511
Down Mesor	0.043	.836	-1.802	161	.073
Width Ratio	0.027	.871	-1.276	161	.204
CAR-R^2	4.751	.031	3.140	54.435	.003
CAR-F	5.246	.023	-0.046	43.692	.964
CAR-$F_{improve}$	0.007	.935	-0.539	161	.591
BRS	0.904	.343	-0.996	173	.321
MAP	0.192	.662	2.134	269	.034
HR	0.800	.372	-0.554	269	.580
CRP	4.458	.036	1.120	179.473	.264
IL-6	0.282	.596	1.700	261	.090
TNF-α	86.930	<.001	15.586	129.528	<.001
EPI	3.895	.050	-0.017	22.618	.986
NE	22.442	<.001	0.306	19.834	.763
PAI-1	0.112	.738	1.117	266	.265
D-Dimer	99.519	<.001	6.332	141.035	<.001
vWF	1.327	.250	1.637	268	.103
IMT-CCA	9.074	.003	-11.092	174.210	<.001
IMT-BIF	6.565	.011	-10.656	178.021	<.001
IMT-INT	10.212	.002	-7.431	161.687	<.001

Note. PSQI = Pittsburgh Sleep Quality Index; TST = Total Sleep Time; Sleep % = Percent Sleep; CAR = Circadian activity rhythm; BRS = baroreflex sensitivity; MAP = mean arterial pressure; HR = heart rate; CRP = C-reactive protein; IL-6 = interleukin-6; TNF-α = tumor necrosis factor alpha; EPI = epinephrine; NE = norepinephrine; PAI-1 = plasminogen activator inhibitor 1; vWF = von Willebrand factor; IMT = intima-media thickness; CCA = common carotid arter; BIF = bifurcation; INT = internal carotid artery.

Table 3. Bivariate Correlations among Sleep Predictor Variables and Vascular Biomarkers and Outcomes

	PSQI	ISI	TST	Slp %	Amp.	Min.	Mesor	Slope	Acrophase	Up Mesor	Down Mesor	Width Ratio	R^2	F stat	F improve
FMD	.037	n/a	-.039	.018	.019	.141	.163	-.095	.175	.183	.125	-.012	-.063	-.179	-.052
MAP	-.039	-.036	.098	.041	-.062	.075	.020	-.038	.020	.051	-.011	-.053	-.006	-.049	-.018
BRS	.093	.127	-.079	.125	.244**	-.197*	.027	-.070	-.141	-.232*	-.025	.184*	.222*	.198*	.185*
HR	-.037	-.166	.050	-.072	-.032	.097	.074	-.010	.106	.117	.068	-.029	-.032	-.116	-.048
IL6	.021	-.010	.064	.017	-.094	.032	-.057	.034	.029	-.005	.049	.054	-.034	-.084	-.073
CRP	.029	.033	.043	-.049	-.144	.116	-.016	.006	.004	.019	-.010	-.026	-.128	-.141	-.135
TNF-α	-.090	-.006	.024	-.036	-.015	.064	.055	.169*	.012	.086	-.052	-.125	.108	-.078	-.096
vWF	-.011	.039	.034	.056	-.188*	-.042	-.226**	.048	-.047	-.018	-.057	-.043	-.202*	-.108	-.143
D-Dimer	-.016	.239**	.017	.021	-.123	.067	-.048	.082	-.006	-.029	.015	.039	-.06	-.148	-.133
PAI-1	.034	.013	-.055	-.123	-.004	.035	.033	-.076	.188*	.191*	.133	-.025	-.045	-.100	-.136
NE	-.041	.350	-.008	-.069	-.025	.249	.227	.096	.012	.027	-.004	-.028	.028	-.034	-.027
EPI	-.070	.246	.059	-.039	.054	.004	.052	-.079	.104	.020	.147	.138	-.078	-.005	-.021
IMT-CCA	.075	.103	.046	-.045	-.149	.069	-.075	-.059	.066	.130	-.002	-.116	-.224*	-.094	-.130
IMT-BIF	.084	.034	.007	-.027	-.099	.066	-.026	-.175	.099	.080	.089	.024	-.139	-.065	.005
IMT-INT	-.028	-.052	.027	.067	-.077	-.038	-.117	-.117	-.110	-.132	-.063	.047	-.171	-.042	-.015

Note. * $p < .05$, ** $p < .01$; PSQI = Pittsburgh Sleep Quality Index; ISI = Insomnia Severity Index; TST = total sleep time; Slp % = percent sleep; FMD = flow-mediated dilation; MAP = mean arterial pressure; BRS = baroreflex sensitivity; HR = heart rate; IL6 = Interleukin 6; CRP = C-reactive protein; TNF-α = Tumor Necrosis Factor alpha; vWF = von Willebrand factor; PAI-1 = plasminogen activator inhibitor 1; NE = norepinephrine; EPI = epinephrine; IMT = intima-media thickness; CCA = common carotid artery; BIF = bifurcation; INT = internal carotid artery.

Table 4. Multiple linear regression model of ISI score predicting D-Dimer

	B	SE	B	*t*	*p*
Constant	283.972	83.020	-	3.421	.001
ISI	4.672	2.491	.169	1.876	.063
BMI	6.378	2.435	.241	2.619	.010
RAPA	-9.437	8.457	-.101	-1.116	.267
RMBC – Frequency	1.268	1.037	.108	1.223	.224

Note: $n = 120$; $df = 4, 115$; $R^2 = .159$; Adjusted $R^2 = .130$

Table 5. Multiple linear regression model of CAR-Amplitude predicting BRS

Full Sample	*B*	SE	B	*t*	*p*
Constant	2.222	4.551	-	.488	.626
Amplitude	3.132	1.756	.178	1.783	.077
BMI	-.140	.090	-.148	-1.557	.122
RAPA	.410	.331	.121	1.238	.219
RMBC – Frequency	.111	.039	.254	2.855	.005

Note: $n = 111$; $df = 4,106$; $R^2 = .170$; Adjusted $R^2 = .139$

Study 1	*B*	SE	B	*t*	*p*
Constant	12.861	29.148	-	.441	.669
Amplitude	9.025	9.641	.342	.936	.374
BMI	-1.073	.618	-.451	-1.736	.117
RAPA	.960	1.711	.193	.561	.589
RMBC – Frequency	.105	.259	.121	.405	.695

Note: $n = 14$; $df = 4,9$; $R^2 = .457$; Adjusted $R^2 = .215$

Study 2	*B*	SE	B	*t*	*p*
Constant	3.680	4.254	-	.865	.389
Amplitude	2.245	1.676	.141	1.340	.184
BMI	-.121	.083	-.152	-1.466	.146
RAPA	.214	.311	.071	.689	.493
RMBC – Frequency	.117	.036	.314	3.272	.002

Note: $n = 97$; $df = 4,92$; $R^2 = .173$; Adjusted $R^2 = .137$

Table 6. Multiple linear regression model of CAR-Minimum predicting BRS

	B	SE	B	*t*	*p*
Constant	8.911	3.155	-	2.825	.006
Minimum	-5.140	2.797	-.166	-1.837	.069
BMI	-.160	.088	-.169	-1.823	.071
RAPA	.555	.312	.164	1.775	.079
RMBC – Frequency	.112	.039	.256	2.879	.005

Note: $n = 111$; $df = 4, 106$; $R^2 = .171$; Adjusted $R^2 = .140$

Table 7. Multiple linear regression model of CAR-Up Mesor predicting BRS

	B	SE	B	*t*	*p*
Constant	15.385	4.340	-	3.545	.001
Up Mesor	-1.163	.417	-.264	-2.788	.006
Sex	1.419	1.192	.107	1.190	.237
BMI	-.196	.086	-.208	-2.273	.025
RAPA	.368	.318	.109	1.158	.249
RMBC – Frequency	.133	.039	.303	3.378	.001

Note: $n = 111$; $df = 5, 105$; $R^2 = .206$; Adjusted $R^2 = .168$

Table 8. Multiple linear regression model of CAR-Width Ratio predicting BRS

	B	SE	B	*t*	*p*
Constant	-1.344	6.172	-	-.218	.828
Width Ratio	15.417	8.669	.162	1.778	.078
BMI	-.183	.087	-.193	-2.099	.038
RAPA	.484	.319	.143	1.516	.133
RMBC – Frequency	.113	.039	.258	2.889	.005

Note: $n = 111$; $df = 4, 106$; $R^2 = .170$; Adjusted $R^2 = .138$

Table 9. Multiple linear regression model of CAR-R^2 predicting BRS

Full Sample	*B*	SE	B	*t*	*p*
Constant	3.344	3.786	-	.883	.379
CAR-R^2	9.973	4.528	.213	2.202	.030
BMI	-.142	.088	-.151	-1.620	.108
RAPA	.379	.326	.112	1.160	.248
RMBC – Frequency	.111	.039	.253	2.869	.005

Note: $n = 111$; $df = 4,106$; $R^2 = .182$; Adjusted $R^2 = .151$

Study 1	*B*	SE	B	*t*	*p*
Constant	29.161	25.011	-	1.166	.274
CAR-R^2	2.782	18.835	.042	.148	.886
BMI	-1.116	.645	-.469	-1.731	.118
RAPA	1.858	1.528	.373	1.216	.255
RMBC – Frequency	.021	.254	.024	.083	.936

Note: $n = 14$; $df = 4,9$; $R^2 = .405$; Adjusted $R^2 = .141$

Study 2	*B*	SE	B	*t*	*p*
Constant	2.392	3.442	-	.695	.489
CAR-R^2	11.997	4.426	.273	2.711	.008
BMI	-.110	.079	-.138	-1.397	.166
RAPA	.073	.306	.024	.240	.811
RMBC – Frequency	.119	.035	.320	3.431	.001

Note: $n = 97$; $df = 4,92$; $R^2 = .219$; Adjusted $R^2 = .185$

Table 10. Multiple linear regression model of CAR-F statistic predicting BRS

Full Sample	*B*	SE	B	*t*	*p*
Constant	6.101	3.277	-	1.862	.065
CAR-F	.001	.001	.186	1.990	.049
BMI	-.151	.088	-.160	-1.721	.088
RAPA	.468	.318	.138	1.471	.144
RMBC – Frequency	.100	.039	.228	2.562	.012

Note: $n = 111$; $df = 4,106$; $R^2 = .177$; Adjusted $R^2 = .138$

Study 1	*B*	SE	B	*t*	*p*
Constant	29.914	23.538	-	1.271	.236
CAR-F	-.001	.004	-.046	-.164	.874
BMI	-1.095	.663	-.460	-1.652	.133
RAPA	2.029	1.501	.407	1.351	.210
RMBC – Frequency	.035	.272	.040	.127	.902

Note: $n = 14$; $df = 4,9$; $R^2 = .406$; Adjusted $R^2 = .141$

Study 2	*B*	SE	B	*t*	*p*
Constant	4.813	2.945	-	1.634	.106
CAR-F	.001	.000	.292	2.984	.004
BMI	-.105	.078	-.132	-1.344	.182
RAPA	.119	.297	.040	.402	.689
RMBC – Frequency	.111	.035	.297	3.204	.002

Note: $n = 97$; $df = 4,92$; $R^2 = .231$; Adjusted $R^2 = .197$

Table 11. Multiple linear regression model of CAR-F improve predicting BRS

	B	SE	B	*t*	*p*
Constant	6.768	3.184	-	2.126	.036
CAR-F improve	.002	.001	.193	2.036	.044
BMI	-.160	.087	-.170	-1.837	.069
RAPA	.398	.327	.118	1.218	.226
RMBC – Frequency	.108	.039	.247	2.792	.006

Note: $n = 111$; $df = 4, 106$; $R^2 = .177$; Adjusted $R^2 = .146$

Table 12. Multiple linear regression model of CAR-Slope predicting TNF-α

Full Sample	*B*	SE	B	*t*	*p*
Constant	-.539	2.098	-	-.257	.798
CAR-Slope	.012	.007	.135	1.816	.072
Age	.038	.024	.121	1.608	.110
BMI	.033	.033	.075	.984	.327
RMBC – Frequency	.075	.020	.407	3.761	.000
RMBC – React	-.102	.017	-.683	-6.142	.000

Note: n = 140; df = 5,134; R^2= .276; Adjusted R^2= .249

Study 1	*B*	SE	B	*t*	*p*
Constant	4.585	4.623	-	.992	.328
CAR-Slope	.055	.018	.424	3.118	.004
Age	.063	.056	.153	1.124	.269
Years Caregiving	-.110	.099	-.157	-1.116	.272
CDR Score	-2.026	.710	-.408	-2.855	.007

Note: n = 39; df = 4,34; R^2= .390; Adjusted R^2= .318

Study 2	*B*	SE	B	*t*	*p*
Constant	-.837	.860	-	-.972	.333
CAR-Slope	.001	.002	.042	.483	.630
Age	.032	.009	.334	3.647	.000
BMI	.019	.012	.148	1.580	.117
RAPA	-.082	.045	-.175	-1.835	.070
CDR Score	.237	.119	.175	1.992	.049

Note: n = 106; df = 5,100; R^2= .247; Adjusted R^2= .209

Table 13. Multiple linear regression model of CAR-Amplitude predicting vWF

Full Sample	*B*	SE	B	*t*	*p*
Constant	-184.560	126.183	-	-1.463	.146
Amplitude	-13.122	26.360	-.044	-.498	.619
Age	3.618	1.083	.282	3.342	.001
BMI	3.484	1.552	.193	2.245	.026

Note: n = 146; df = 3,142; R^2= .185; Adjusted R^2= .146

Study 1	*B*	SE	B	*t*	*p*
Constant	67.976	255.249	-	.266	.792
Amplitude	15.078	42.248	.067	.357	.723
Age	.255	2.257	.021	.113	.911
BMI	.778	3.872	.035	.201	.842

Note: n = 39; df = 3,35; R^2= .004; Adjusted R^2= -.081

Study 2	*B*	SE	B	*t*	*p*
Constant	-225.433	146.105	-	-1.543	.126
Amplitude	-27.951	33.143	-.085	-.843	.401
Age	4.639	1.226	.360	3.785	.000
BMI	3.407	1.706	.196	1.997	.048

Note: n = 107; df = 3,103; R^2= .188; Adjusted R^2= .165

Table 14. Multiple linear regression model of CAR-Mesor predicting vWF

Full Sample	*B*	SE	B	*t*	*p*
Constant	-33.154	120.305	-	-.276	.783
Mesor	-113.555	47.716	-.194	-2.380	.019
Age	3.120	1.039	.243	3.002	.003
BMI	3.138	1.431	.174	2.192	.030

Note: n = 146; df = 3,142; R^2= .151; Adjusted R^2= .133

Study 1	*B*	SE	B	*t*	*p*
Constant	262.429	234.072	-	1.121	.270
Mesor	-73.466	75.572	-.168	-.972	.338
Age	-.545	2.119	-.044	-.257	.799
BMI	-.044	3.710	-.002	-.012	.991

Note: n = 39; df = 3,35; R^2= .027; Adjusted R^2= -.057

Study 2	*B*	SE	B	*t*	*p*
Constant	-106.821	142.797	-	-.748	.456
Mesor	-122.916	60.981	-.188	-2.016	.046
Age	4.238	1.193	.329	3.551	.001
BMI	3.402	1.559	.195	2.182	.031

Note: n = 107; df = 3,103; R^2= .214; Adjusted R^2= .191

Table 15. Multiple linear regression model of CAR-R^2 predicting vWF

Full Sample	*B*	SE	B	*t*	*p*
Constant	-139.236	110.747	-	-1.257	.211
CAR-R^2	-91.251	67.151	-.116	-1.359	.176
Age	3.398	1.055	.265	3.220	.002
BMI	3.102	1.509	.172	2.055	.042

Note: n = 146; df = 3,142; R^2= .128; Adjusted R^2= .110

Study 1	*B*	SE	B	*t*	*p*
Constant	276.432	240.584	-	1.149	.258
CAR-R^2	-111.926	112.508	-.185	-.995	.327
Age	-.853	2.207	-.069	-.387	.701
BMI	-.808	3.875	-.037	-.208	.836

Note: n = 39; df = 3,35; R^2= .028; Adjusted R^2= -.055

Study 2	*B*	SE	B	*t*	*p*
Constant	-254.041	126.848	-	-2.003	.048
CAR-R^2	-68.160	86.788	-.076	-.785	.434
Age	4.715	1.205	.366	3.912	.000
BMI	3.589	1.641	.206	2.187	.031

Note: n = 107; df = 3,103; R^2= .188; Adjusted R^2 = .164

Table 16. Multiple linear regression model of CAR-Acrophase predicting PAI-1

	B	SE	B	*t*	*p*
Constant	9.639	62.665	-	.183	.855
Acrophase	5.518	2.535	.178	2.177	.031
Age	-1.008	.372	-.225	-2.711	.008
BMI	1.334	.542	.214	2.459	.015
RAPA	-3.795	1.818	-.180	-2.088	.039
RMBC – React	-.071	.181	-.033	-.389	.698

Note: $n = 139$; $df = 5, 133$; $R^2 = .178$; Adjusted $R^2 = .147$

Table 17. Multiple linear regression model of CAR-Up Mesor predicting PAI-1

	B	SE	B	*t*	*p*
Constant	40.575	37.235	-	1.090	.278
Up Mesor	4.997	2.248	.174	2.223	.028
Age	-.927	.352	-.210	-2.634	.009
BMI	1.439	.505	.232	2.848	.005
RAPA	-3.036	1.682	-.150	-1.805	.073

Note: $n = 146$; $df = 4, 141$; $R^2 = .167$; Adjusted $R^2 = .144$

Table 18. Multiple linear regression model of CAR-R^2 predicting IMT-CCA

Full Sample	*B*	SE	B	*t*	*p*
Constant	.267	.226	-	1.181	.240
CAR-R^2	-.182	.154	-.098	-1.178	.241
Age	.009	.002	.305	3.647	.000
RMBC – React	.005	.001	.375	4.615	.000

Note: n = 128; df = 3,124; R^2 = .235; Adjusted R^2 = .216

Study 1	*B*	SE	B	*t*	*p*
Constant	.304	.268	-	1.134	.265
CAR-R^2	.008	.151	.009	.056	.955
Age	.006	.003	.336	2.022	.051
RMBC – React	.002	.002	.153	.966	.340

Note: n = 39; df = 3,35; R^2= .138; Adjusted R^2= .064

Study 2	*B*	SE	B	*t*	*p*
Constant	.225	.261	-	.862	.391
CAR-R^2	.014	.204	.007	.070	.944
Age	.010	.003	.403	3.779	.000
RMBC – React	.002	.001	.151	1.487	.141

Note: n = 89; df = 3,85; R^2= .159; Adjusted R^2= .129

Table 19. Longitudinal Study Characteristics – Caregivers

	Year 1 *n* = 126	Year 2 *n* = 93	Year 3 *n* = 64	Year 4 *n* = 38	Year 5 *n* = 7
Patient Characteristics					
Gender					
Men	37 (29.4%)	32 (34.4%)	20 (31.3%)	14 (36.8%)	4 (57.1%)
Women	89 (70.6%)	61 (65.6%)	44 (68.8%)	24 (63.2%)	3 (42.9%)
Race/Ethnicity					
Black or African American	3 (2.4%)	3 (3.2%)	3 (4.7%)	2 (5.3%)	0 (0.0%)
American Indian or Alaskan Native	2 (1.6%)	2 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Pacific Islander	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	120 (95.2%)	88 (94.6%)	61 (95.3%)	36 (94.7%)	7 (100%)
Age, years	74.15 (7.94)	76.00 (7.78)	77.74 (7.30)	78.13 (6.96)	78.72 (8.35)
Years Caregiving	4.33 (3.39)	5.47 (3.77)	6.13 (3.17)	7.17 (3.26)	12.16 (6.09)
CDR Score	1.64 (0.65)	1.73 (0.68)	2.02 (0.75)	2.23 (0.67)	2.50 (0.55)
RMBC – Frequency	34.67 (12.99)	33.52 (12.71)	29.84 (11.81)	31.33 (17.23)	30.83 (11.55)
RMBC – React	14.08 (11.81)	12.97 (13.00)	10.29 (9.20)	11.79 (11.72)	10.67 (11.17)
CESD	8.73 (5.80)	8.11 (5.55)	8.76 (6.16)	8.32 (5.71)	9.17 (5.38)
PA	31.79 (7.43)	31.69 (6.44)	31.92 (7.21)	32.42 (6.90)	34.5 (4.51)
NA	17.96 (6.03)	16.70 (5.70)	17.57 (7.82)	16.89 (6.09)	17.5 (8.26)
RAPA	3.42 (1.64)	3.02 (1.33)	2.83 (1.67)	2.87 (1.74)	2.57 (1.81)
BMI	26.49 (4.71)	27.05 (5.22)	26.73 (5.24)	26.62 (4.53)	26.58 (3.86)
Sleep Variables					
PSQI Score	6.69 (3.57)	6.14 (3.58)	6.66 (3.48)	6.15 (3.85)	7.00 (3.10)
Actigraphy Total Sleep Time, hours	7.30 (1.13)	7.33 (1.09)	7.31 (0.94)	6.99 (1.09)	7.28 (1.02)
Actigraphy Sleep Efficiency, %	87.31 (5.35)	87.11 (6.12)	88.35 (4.89)	86.47 (6.69)	88.69 (5.04)
Vascular Variables					
BRS, ms/mmHg	8.31 (7.47)	7.68 (4.56)	9.25 (11.38)	27.87 (42.61)	*
MAP, mmHg	95.32 (9.62)	92.02 (10.25)	89.34 (10.70)	92.42 (11.08)	91.11 (7.02)
Resting Heart Rate, bpm	65.99 (10.00)	65.69 (10.54)	63.70 (9.30)	62.91 (9.44)	64.67 (10.64)
CRP, mg/L	3.70 (6.34)	5.48 (17.94)	4.37 (5.79)	3.73 (6.15)	2.63 (1.35)
IL6, pg/mL	1.51 (2.00)	2.52 (5.56)	1.98 (2.90)	1.55 (0.76)	1.43 (0.75)
TNF-α, pg/mL	6.12 (2.70)	5.85 (2.74)	5.75 (4.15)	6.77 (2.13)	4.79 (1.33)
EPI, pg/mL	42.67 (42.95)	90.43 (94.66)	96.81 (90.81)	54.40 (12.05)	*
NE, pg/mL	510.21 (243.30)	601.91 (327.16)	552.38 (208.48)	373.38 (115.33)	*
PAI-1, ng/mL	36.71 (30.12)	31.34 (30.26)	28.13 (24.12)	28.07 (20.45)	25.29 (31.70)
D-Dimer, ng/mL	768.16 (430.41)	806.25 (489.53)	659.12 (307.06)	656.82 (333.16)	710.76 (308.16)
vWF, mg/dL	176.64 (109.31)	181.99 (98.56)	140.19 (62.83)	152.05 (54.14)	166.76 (31.12)
FMD, % increase	11.00 (4.22)	10.67 (4.30)	9.15 (5.57)	9.14 (2.59)	11.58 (1.30)
IMT – CCA, mm	0.80 (0.14)	0.86 (0.20)	0.89 (0.18)	*	*

Note. * denotes that insufficient data were available to calculate a mean and standard deviation; CDR = Clinical Dementia Rating; RMBC = Revised Memory and Behavior Checklist; CESD = Center for Epidemiological Studies-Depression; PA = positive affect; NA = negative affect; RAPA = Rapid Assessment of Physical Activity; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; CRP = C-reactive protein; IL6 = Interleukin-6; TNF-α = Tumor Necrosis Factor alpha; EPI = epinephrine; NE = norepinephrine; PAI-1 = plasminogen activator inhibitor 1; vWF = von Willebrand factor; FMD = flow-mediated dilation; IMT = intima-media thickness; CCA = common carotid artery.

Table 20. Longitudinal Study Characteristics – Non-Caregivers

	Year 1 *n* = 60	Year 2 *n* = 55	Year 3 *n* = 49	Year 4 *n* = 39	Year 5 *n* = 12
Patient Characteristics					
Gender					
Men	20 (33.3%)	17 (30.9%)	17 (34.7%)	11 (28.2%)	2 (16.7%)
Women	40 (66.7%)	38 (69.1%)	32 (65.3%)	28 (71.8%)	10 (83.3%)
Race/Ethnicity					
Black or African American	2 (3.3%)	2 (3.6%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Asian	6 (10.0%)	5 (9.1%)	4 (8.2%)	2 (5.1%)	0 (0.0%)
White	52 (86.7%)	48 (87.3%)	44 (89.8%)	37 (94.9%)	12 (100%)
Age, years	74.49 (6.45)	77.54 (5.96)	75.68 (5.79)	76.34 (5.59)	75.35 (5.67)
CDR Score	0.11 (0.25)	0.13 (0.24)	0.17 (0.35)	0.13 (0.25)	0.21 (0.26)
RMBC – Frequency	5.93 (6.39)	5.93 (7.46)	8.65 (9.33)	6.90 (8.40)	8.83 (10.19)
RMBC – React	2.35 (3.85)	2.02 (3.79)	2.65 (3.84)	2.54 (4.51)	4.08 (4.34)
CESD	2.67 (4.10)	2.55 (3.26)	3.51 (3.78)	3.87 (3.37)	4.08 (3.00)
PA	36.70 (6.59)	35.15 (5.73)	35.32 (6.24)	35.15 (6.97)	34.25 (6.08)
NA	13.68 (5.13)	13.25 (3.89)	13.51 (3.45)	13.54 (3.28)	13.92 (3.92)
RAPA	4.00 (1.52)	3.83 (1.57)	3.65 (1.52)	3.72 (1.65)	2.92 (1.83)
BMI	26.16 (5.95)	25.65 (5.12)	25.87 (5.47)	25.63 (5.71)	26.00 (6.38)
Sleep Variables					
PSQI Score	4.60 (2.57)	4.47 (2.60)	5.11 (3.02)	4.90 (2.87)	5.00 (1.86)
Actigraphy Total Sleep Time	6.92 (0.93)	7.00 (1.02)	6.97 (0.97)	7.01 (0.81)	6.45 (0.81)
Actigraphy Sleep Efficiency	87.52 (5.53)	87.10 (5.73)	87.59 (5.78)	87.33 (5.73)	87.20 (4.63)
Vascular Variables					
Baroreflex Sensitivity	9.74 (5.56)	8.99 (5.12)	9.84 (6.74)	6.78 (2.88)	*
Mean Arterial Pressure	93.12 (10.95)	91.31 (10.05)	90.93 (8.84)	87.91 (9.84)	88.94 (8.28)
Resting Heart Rate	65.11 (9.61)	61.80 (8.35)	63.19 (8.87)	62.05 (9.71)	66.63 (11.48)
CRP	3.29 (7.90)	3.78 (4.75)	3.05 (4.85)	4.10 (12.04)	4.52 (4.85)
IL6	2.06 (2.59)	1.76 (2.76)	2.11 (3.18)	2.25 (2.28)	3.38 (5.79)
TNF-α	5.96 (2.09)	4.63 (2.05)	9.08 (30.04)	6.05 (1.90)	5.40 (1.40)
EPI	31.30 (15.57)	83.89 (80.21)	91.28 (63.19)	63.53 (19.20)	*
NE	481.66 (185.26)	576.94 (284.20)	574.09 (229.39)	387.55 (98.96)	*
PAI-1	31.71 (30.50)	24.29 (23.00)	27.15 (22.70)	20.65 (14.13)	18.32 (22.06)
D-Dimer	833.88 (547.74)	771.97 (477.94)	651.44 (361.23)	589.43 (349.93)	577.89 (225.19)
vWF	166.04 (125.70)	171.16 (98.93)	132.90 (47.64)	138.10 (46.53)	135.82 (52.10)
FMD	11.19 (3.68)	10.76 (4.16)	10.85 (6.10)	8.87 (3.14)	7.93 (2.89)
IMT – CCA	0.82 (0.19)	0.86 (0.18)	0.86 (0.19)	*	*

Note. CDR = Clinical Dementia Rating; RMBC = Revised Memory and Behavior Checklist; CESD = Center for Epidemiological Studies-Depression; PA = positive affect; NA = negative affect; RAPA = Rapid Assessment of Physical Activity; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; CRP = C-reactive protein; IL6 = Interleukin-6; TNF-α = Tumor Necrosis Factor alpha; EPI = epinephrine; NE = norepinephrine; PAI-1 = plasminogen activator inhibitor 1; vWF = von Willebrand factor; FMD = flow-mediated dilation; IMT = intima-media thickness; CCA = common carotid artery.

Table 21. Multilevel Models of PSQI Scores Predicting FMD

Intercepts and Means as Outcomes Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	11.258	0.326	34.496	0.0000
Time (γ_{10})	-0.584	0.187	-3.130	0.0020
PSQI (γ_{11})	0.179	0.085	2.115	0.0355
PSQIxCGstatus (γ_{12})	-0.299	0.113	-2.639	0.0089
Random Effects				
Intercept (u_{0i})	2.009			
Time (u_{1i})	0.0002			
Residual (ε_{it})	3.861			
AIC = 2271.471, BIC = 2303.159, logLik = -1127.735, Observations: 392, Groups: 166				

Covariate Adjusted Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	11.329	0.327	34.671	0.0000
Time (γ_{10})	-0.592	0.190	-3.122	0.0020
PSQI (γ_{11})	0.166	0.088	1.886	0.0605
PSQIxCGstatus (γ_{12})	-0.302	0.113	-2.678	0.0080
RMBC Reaction (γ_{13})	0.010	0.019	0.525	0.6004
Random Effects				
Intercept (u_{0i})	1.996			
Time (u_{1i})	0.0003			
Residual (ε_{it})	3.839			
AIC = 2262.482, BIC = 2298.061, logLik = -1122.241, Observations: 390, Groups: 164				

Table 22. Multilevel Model of PSQI Scores Predicting BRS

Intercepts and Means as Outcomes Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	8.240	0.666	12.363	0.0000
Time (γ_{10})	0.533	0.638	0.835	0.4050
PSQI (γ_{11})	-0.271	0.136	-1.997	0.0476
Random Effects				
Intercept (u_{0i})	5.891			
Time (u_{1i})	6.147			
Residual (ε_{it})	4.278			
AIC = 2054.568, BIC = 2080.541, logLik = -1020.284, Observations: 305, Groups: 155				

Covariate Adjusted Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	8.306	0.659	12.595	0.0000
RAPA (γ_{01})	1.024	0.305	3.353	0.0010
Time (γ_{10})	2.015	0.839	2.402	0.0175
PSQI (γ_{11})	-0.202	0.125	-1.613	0.1088
Age (γ_{12})	0.181	0.054	3.361	0.0010
Sex (γ_{13})	-2.121	0.815	-2.603	0.0102
Random Effects				
Intercept (u_{0i})	5.840			
Time (u_{1i})	5.819			
Residual (ε_{it})	4.247			
AIC = 2034.337, BIC = 2071.342, logLik = -1007.169, Observations: 305, Groups: 155				

Table 23. Multilevel Model of Actigraphy Percent Sleep Predicting BRS

Intercepts and Means as Outcomes Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	8.132	0.678	11.999	0.0000
Time (γ_{10})	0.519	0.655	0.793	0.4294
Slp% (γ_{11})	-0.151	0.128	-1.179	0.2404
Slp% by CG Status (γ_{12})	0.346	0.171	2.025	0.0447
Random Effects				
Intercept (u_{0i})	5.922			
Time (u_{1i})	6.304			
Residual (ε_{it})	4.296			

AIC = 2019.014, BIC = 2048.409, logLik = -1001.507, Observations: 299, Groups: 152

Covariate Adjusted Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	8.209	0.674	12.178	0.0000
RAPA (γ_{01})	1.012	0.305	3.318	0.0011
Time (γ_{10})	2.220	0.860	2.582	0.0108
Slp% (γ_{11})	0.063	0.080	0.792	0.4298
Age (γ_{12})	0.163	0.054	3.002	0.0032
Sex (γ_{13})	-2.417	0.835	-2.896	0.0044
Random Effects				
Intercept (u_{0i})	5.929			
Time (u_{1i})	6.013			
Residual (ε_{it})	4.247			

AIC = 1999.057, BIC = 2035.859, logLik = -989.529, Observations: 299, Groups: 152

Table 24. Multilevel Model of Actigraphy Percent Sleep Predicting HR

Intercepts and Means as Outcomes Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	65.486	0.703	93.183	0.0000
Slp% (γ_{01})	-0.379	0.140	-2.702	0.0076
Time (γ_{10})	-0.909	0.299	-3.040	0.0025
SE (γ_{11})	0.183	0.068	2.686	0.0076
Random Effects				
Intercept	8.129			
Time	2.171			
Residual	5.171			

AIC = 3630.985, BIC = 3664.985, logLik = -1807.493, Observations: 522, Groups: 176

Covariate Adjusted Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	63.785	1.245	51.222	0.0000
Slp% (γ_{01})	-0.379	0.141	-2.696	0.0077
RAPA (γ_{02})	-0.903	0.482	-1.872	0.0629
RMBC Reaction (γ_{03})	0.096	0.063	1.514	0.1319
Sex (γ_{04})	2.321	1.528	1.518	0.1308
Time (γ_{10})	-1.802	0.510	-3.534	0.0005
Slp% (γ_{11})	0.158	0.067	2.373	0.0182
Sex (γ_{12})	1.392	0.624	2.231	0.0263
Random Effects				
Intercept (u_{0i})	8.009			
Time (u_{1i})	2.048			
Residual (ε_{it})	5.201			

AIC = 3604.827, BIC = 3655.687, logLik = -1790.414, Observations: 520, Groups: 174

Table 25. Multilevel Model of Actigraphy Percent Sleep Predicting NE

Intercepts and Means as Outcomes Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	547.002	16.971	32.231	0.0000
Slp% (γ_{01})	5.171	2.418	2.138	0.0339
Time (γ_{10})	-14.169	11.641	-1.217	0.2245
Random Effects				
Intercept (u_{0i})	0.013			
Time (u_{1i})	0.007			
Residual (ε_{it})	250.725			
AIC = 6465.062, BIC = 6494.026, logLik = -3225.531, Observations: 466, Groups: 176				

Covariate Adjusted Model				
	Value	Standard Error	t-value	p-value
Fixed Effects				
Intercept (γ_{00})	546.612	17.140	31.891	0.0000
Slp% (γ_{01})	4.970	2.445	2.033	0.0436
RMBC Reaction (γ_{02})	0.657	1.218	0.540	0.5901
Time (γ_{10})	-27.872	16.875	-1.652	0.0997
Sex (γ_{11})	20.627	17.345	1.189	0.235
Random Effects				
Intercept (u_{0i})	0.001			
Time (u_{1i})	0.001			
Residual (ε_{it})	251.327			
AIC = 6431.712, BIC = 6468.873, logLik = -3206.856, Observations: 464, Groups: 174				

Table 26. Intervention Study Characteristics

Condition	Pre-Treatment		Post-Treatment		6 Month Follow-up		12 Month Follow-up	
	BA	IS	BA	IS	BA	IS	BA	IS
	n = 75	*n* = 75	*n* = 64	*n* = 68	*n* = 52	*n* = 56	*n* = 45	*n* = 43
Patient Characteristics								
Gender								
Men	16 (21.3%)	18 (24.0%)	13 (20.3%)	16 (23.5%)	10 (19.6%)	12 (21.8%)	10 (22.7%)	7 (18.4%)
Women	59 (78.7%)	57 (76.0%)	51 (79.7%)	52 (76.5%)	41 (80.4%)	43 (78.2%)	34 (77.3%)	31 (81.6%)
Race/Ethnicity								
Black or African American	2 (2.7%)	4 (5.4%)	1 (1.6%)	4 (6.0%)	1 (1.9%)	4 (7.1%)	1 (2.2%)	2 (5.0%)
American Indian/ Alaskan Native	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	2 (2.7%)	3 (4.1%)	1 (1.6%)	3 (4.5%)	1 (1.9%)	2 (3.6%)	0 (0.0%)	2 (5.0%)
Native Hawaiian/ Pacific Islander	2 (2.7%)	2 (2.7%)	2 (3.1%)	2 (3.0%)	2 (3.8%)	2 (3.6%)	2 (4.4%)	2 (5.0%)
White	69 (92.0%)	64 (86.5%)	60 (93.8%)	57 (85.1%)	48 (92.3%)	48 (85.7%)	42 (93.3%)	34 (85.0%)
Age, years	73.02 (7.96)	73.97 (8.04)	72.90 (7.34)	73.82 (7.68)	74.20 (7.22)	73.68 (7.96)	74.75 (7.22)	74.83 (8.24)
Years Caregiving	4.91 (3.53)	4.34 (2.89)	5.23 (3.69)	4.40 (2.95)	5.20 (3.80)	4.40 (3.07)	5.02 (3.52)	4.47 (3.03)
CDR Score	1.38 (0.58)	1.40 (0.60)	1.52 (0.64)	1.50 (0.64)	1.67 (0.69)	1.69 (0.63)	1.87 (0.62)	1.94 (0.61)
RMBC – Frequency	35.72 (12.84)	37.18 (14.16)	34.65 (14.01)	33.73 (11.37)	36.98 (11.91)	32.52 (12.39)	34.62 (13.49)	33.28 (10.02)
RMBC – React	33.18 (16.72)	33.15 (14.86)	28.90 (16.63)	25.94 (12.60)	32.15 (15.43)	24.93 (11.31)	29.03 (16.44)	24.34 (10.64)
CESD	17.08 (8.84)	16.59 (7.83)	15.36 (9.48)	14.62 (8.08)	15.51 (9.32)	14.32 (7.88)	15.82 (10.36)	14.62 (8.39)
ZBI	34.69 (8.65)	32.63 (7.14)	33.22 (8.61)	30.49 (6.58)	31.60 (8.94)	29.97 (7.33)	30.78 (9.00)	29.28 (8.80)
PA	32.93 (7.51)	33.45 (6.81)	33.93 (7.12)	34.31 (6.58)	33.95 (7.06)	33.49 (6.96)	32.70 (7.55)	34.21 (6.11)
NA	20.89 (7.29)	21.61 (6.27)	19.18 (6.68)	19.04 (6.32)	18.33 (6.49)	18.86 (6.48)	18.23 (7.38)	19.13 (6.62)
RAPA	3.27 (1.70)	3.49 (1.66)	3.42 (1.89)	3.65 (1.51)	3.15 (1.64)	2.93 (2.02)	3.31 (1.69)	2.95 (1.89)
BMI	27.81 (5.64)	27.18 (6.11)	27.44 (5.22)	27.50 (6.32)	27.65 (4.77)	26.86 (4.64)	27.88 (5.09)	27.15 (4.55)

Table 26. Intervention Study Characteristics Continued

Condition	Pre-Treatment		Post-Treatment		6 Month Follow-up		12 Month Follow-up	
	BA	IS	BA	IS	BA	IS	BA	IS
	n = 75	*n* = 75	*n* = 64	*n* = 68	*n* = 52	*n* = 56	*n* = 45	*n* = 43
Sleep Variables								
PSQI Score	7.31 (3.80)	7.34 (3.29)	6.15 (3.65)	7.13 (3.69)	6.33 (3.19)	6.59 (3.13)	6.73 (3.67)	8.17 (3.49)
Total ISI Score	7.62 (5.67)	7.92 (5.42)	5.86 (4.87)	6.91 (5.33)	6.00 (5.26)	6.06 (5.76)	5.93 (5.62)	8.00 (6.16)
Actigraphy Total Sleep Time*	7.13 (1.07)	7.61 (1.26)	7.10 (1.05)	7.54 (1.16)	7.20 (0.91)	7.48 (1.18)	7.10 (1.37)	7.47 (1.28)
Actigraphy Sleep Efficiency	86.93 (5.93)	87.23 (5.05)	86.62 (7.19)	88.06 (4.15)	87.51 (4.51)	87.33 (5.64)	85.70 (12.15)	88.89 (4.49)
CAR – Amplitude	1.69 (0.34)	1.70 (0.28)	1.69 (0.32)	1.75 (0.27)	1.70 (0.31)	1.70 (0.24)	1.65 (0.37)	1.71 (0.25)
CAR – Minimum	0.24 (0.19)	0.26 (0.18)	0.26 (0.21)	0.24 (0.17)	0.28 (0.22)	0.25 (0.19)	0.31 (0.28)	0.24 (0.12)
CAR – Mesor	1.08 (0.16)	1.11 (0.16)	1.10 (0.18)	1.11 (0.13)	1.14 (0.17)	1.11 (0.13)	1.13 (0.21)	1.09 (0.12)
CAR – Slope*	19.77 (23.22)	12.53 (9.87)	16.37 (18.48)	11.42 (9.52)	21.12 (29.90)	11.40 (7.30)	24.06 (47.67)	13.24 (13.25)
CAR – Acrophase	14.51 (1.09)	14.64 (1.13)	14.63 (1.05)	14.63 (0.99)	15.08 (1.80)	14.56 (1.10)	14.84 (1.34)	14.65 (0.85)
CAR – Up-Mesor	6.77 (1.25)	7.20 (1.16)	6.90 (1.26)	7.10 (1.06)	7.39 (1.83)	7.04 (1.04)	7.20 (1.06)	7.03 (0.89)
CAR – Down-Mesor	22.25 (1.44)	22.08 (1.44)	22.34 (1.12)	22.17 (1.36)	22.77 (1.95)	22.09 (1.64)	22.48 (2.08)	22.26 (1.18)
CAR – Width Ratio*	0.64 (0.07)	0.62 (0.05)	0.64 (0.05)	0.63 (0.06)	0.64 (0.05)	0.63 (0.07)	0.64 (0.08)	0.63 (0.05)
CAR – R squared	0.42 (0.12)	0.44 (0.11)	0.42 (0.11)	0.45 (0.10)	0.44 (0.10)	0.43 (0.09)	0.41 (0.14)	0.43 (0.10)
CAR – F statistic	2010.61 (1237.09)	2153.82 (1169.80)	1920.96 (954.08)	2173.94 (870.83)	2121.00 (961.62)	1908.26 (767.14)	1990.79 (1294.12)	1935.13 (799.73)
CAR – F improve	814.82 (708.27)	686.75 (519.81)	660.56 (503.07)	660.18 (418.25)	667.69 (512.61)	597.76 (370.55)	734.36 (677.35)	572.25 (333.03)

Note. * denotes significant difference in means for variable between BA and IS support condition; BA = Behavioral Activation; IS = Information Support; CDR = Clinical Dementia Rating; RMBC = Revised Memory and Behavior Checklist; CESD = Center for Epidemiological Studies-Depression; ZBI = Zarit Burden Inventory; PA = positive affect; NA = negative affect; RAPA = Rapid Assessment of Physical Activity; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; ISI = Insomnia Severity Index; CAR = circadian activity rhythm.

Table 27. Pre-Post ANOVAs for Sleep Outcomes by Condition

		n	Mean	Std. Deviation	*F*	*df*	*p*-value
PSQI	BA	62	-0.702	2.546	-1.055	(1, 128)	.293
	IS	68	-0.150	3.326			
ISI	BA	61	-1.552	4.678	-0.394	(1, 127)	.694
	IS	68	-1.221	4.840			
TST	BA	35	-0.031	0.627	-0.139	(1, 70)	.890
	IS	37	-0.020	1.094			
Sleep Efficiency	BA	35	-0.120	3.087	-1.073	(1, 70)	.287
	IS	37	0.744	3.696			
Amplitude	BA	39	-0.048	0.223	-1.193	(1, 76)	.236
	IS	39	0.012	0.222			
Minimum	BA	39	0.036	0.149	1.405	(1, 76)	.164
	IS	39	-0.011	0.148			
Mesor	BA	39	0.012	0.115	0.716	(1, 76)	.476
	IS	39	-0.005	0.095			
Slope	BA	39	-3.018	12.985	-1.193	(1, 76)	.236
	IS	39	0.100	9.880			
Acrophase	BA	39	0.061	0.475	-0.338	(1, 76)	.737
	IS	39	0.100	0.550			
Up-Mesor	BA	39	-0.047	0.595	-0.344	(1, 76)	.732
	IS	39	-0.001	0.596			
Down-Mesor	BA	39	0.169	0.882	-0.147	(1, 76)	.884
	IS	39	0.201	1.053			
Width Ratio	BA	39	0.009	0.049	0.050	(1, 76)	.960
	IS	39	0.008	0.055			
R Squared	BA	39	-0.002	0.061	-0.194	(1, 76)	.847
	IS	39	0.002	0.087			
F Statistic	BA	39	-85.193	573.986	-0.610	(1, 76)	.544
	IS	39	10.034	787.968			
F Improve	BA	39	-41.149	352.907	-0.191	(1, 76)	.849
	IS	39	-21.798	524.207			

Note. PSQI = Pittsburgh Sleep Quality Index; ISI = Insomnia Severity Index; TST = total sleep time.