# Psychobehavioral Factors and Cardiovascular Disease Risk in Family Caregivers

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A Dissertation presented to the Graduate Faculty of
The University of Virginia in Candidacy for the Degree of Doctor of Philosophy

Graduate School of Arts and Sciences
School of Nursing

University of Virginia
August, 2022

## Dedication

I dedicate this dissertation to my family who has been a constant source of support and encouragement throughout the doctoral program.

## Acknowledgements

As I reflect on my journey of doctoral pursuits, I am very appreciative of how much I have been supported by people around me. I acknowledge that anything would never have been possible just on my own. First of all, I would like to express my sincere gratitude to my dissertation committee chair and academic advisor, Dr. Jeongok Logan for her unfailing guidance, consistent support, and unceasing patience. Nothing would have been accomplished during the doctoral program without her tireless advising to me. I have learned from her how to find a silver lining, avoid falling down the rabbit hole, and bounce back from failure. All of these will remain as invaluable assets for me both personally and professionally. I would like to extend my sincere appreciation to my committee members. Thank you to Dr. Jill Howie-Esquivel who always was willing to share her expertise in cardiovascular research with me and provide me with support in many ways throughout the dissertation research project. Thank you to Dr. Misook Chung who enthusiastically offered me advice and guidance in my dissertation research as well as my research career development. Further, thank you to Dr. Eric Davis for providing me with consistent support and critical comments on my work since the development phase of my dissertation project. Finally, thank you to Dr. Jennifer Lobo for committing her time and effort to guiding me with patience in utilizing a new approach to analyzing data.

In sincere gratitude to all my study participants, I am especially thankful for contributing their time and sharing caregiving experience with me. This dissertation would not be possible without their willingness to help science for other caregivers. Thank you to Susan Dietrich, Dr. Mary Crandall, and Dr. Heather Lothamer for their support for recruitment. I would also like to thank the community of the UVA School of Nursing for its tangible and intangible supports and resources that made my experience during the doctoral program very valuable. To my fellow doctoral students, I am very grateful for always reminding me that I am not alone and we are good enough. Finally, very special gratitude goes to my family and friends in Korea for always being there for me and sending me their unconditional support, love, and prayers.

## Funding Sources

This research was supported by the Council for the Advancement of Nursing Science/Southern Nursing Research Society (CANS/SNRS) Dissertation Research Grant, Global Korean Nursing Foundation-USA Scholarship Award, and Barbara Parker Dissertation Funding Award.

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## Abstract

Increased cardiovascular disease (CVD) risk in family caregivers is well documented. Caregivers' vulnerability to declines in cardiovascular health may be attributed to psychological symptoms and alterations in health behavior resulting from caregiving demands. Subclinical CVD markers have shown prognostic significance in various populations, yet caregivers have rarely been assessed for their CVD risk using the surrogate markers. Therefore, the goal of this study is to investigate the relationships among psychological and behavioral factors and CVD risk, represented by a subclinical marker in caregivers of patients with chronic illnesses. To achieve this goal, three manuscripts are presented.

The first manuscript presents a systematic review of 41 articles on CVD risk in caregivers, summarizing current evidence documenting the prevalence of CVD incidence and risk, measures that assess the outcomes, and factors associated with increased CVD risk. The synthesized findings demonstrated that CVD incidence rates were higher among caregivers than non-caregivers and several measures indicated caregivers' greater CVD risk. Factors associated with increased CVD risk included caregiving characteristics, psychological symptoms, and sleep status. This review suggested the importance of modifiable factors related to these characteristics in developing interventions aimed at alleviating CVD risk in the caregiver population.

The second and third manuscripts were derived from a pilot cross-sectional study that assessed psychological symptoms, objective sleep quality, and CVD risk as represented by short-term blood pressure variability (BPV) of family caregivers who provided in-home care for patients with chronic illness. In the second manuscript, the impacts of psychological symptoms (i.e., caregiving stress, depression, and anxiety) on patterns of sleep state transitions were examined using Markov chain models. The results showed that: (1) Caregivers tended to have consistent sleep efficiency states with a relatively small extent of recovery following a night of suboptimal sleep efficiency; and (2) Caregivers' depression and anxiety modified the short- and long-term dynamics of sleep efficiency. The third manuscript examines the associations of psychological symptoms (caregiving stress and depression) and sleep quality (sleep efficiency, wake after sleep onset, and number of awakenings) with short-term BPV. The findings

indicated that greater number of awakenings were significantly associated with increased systolic BPV independent of age and mean arterial pressure; psychological symptoms did not demonstrate a significant relationship.

This pilot cross-sectional study suggests that disrupted sleep represented by frequent awakenings may be linked to caregivers' increased CVD risk. Healthcare providers should pay more attention to caregivers' sleep and cardiovascular health. In addition to improving psychological health for caregivers' sleep quality, providing appropriate support to help them maintain optimal sleep status should be reflected in strategies for alleviating CVD risk in this population. Better understanding of psychobehavioral factors associated with CVD risk can facilitate the development of interventions promoting healthy behavior and self-care practices for caregivers.

**Keywords**: Caregivers, Cardiovascular Diseases, Heart Disease Risk Factors, Behavioral Symptoms, Sleep Quality

# Table of Contents

# Chapter 1: Introduction

## Background

### *Family Caregiving*

As society ages, there has been a consistent increase in demand for home care for individuals living with chronic illness. According to a 2020 report by the National Alliance for Caregiving, nearly one-fifth of American adults (approximately 53 million) are providing unpaid, informal care to their loved ones with chronic illness or disabilities (National Alliance for Caregiving and AARP, 2020). The number is projected to increase as more people are living longer with chronic health conditions. According to a report by the American Association of Retired Persons (AARP) Public Policy Institute, 41 million family caregivers contributed the estimated economic value of $470 billion through 34 billion hours of care to adults with limitations in daily activities in 2017 (Reinhard et al., 2019). Thus, caregiving is no longer just a personal experience but a critical public health issue that affects a large portion of the population.

Family caregivers provided a wide array of care and assistance for individuals with chronic health conditions or disabilities. Caregiving tasks include assistance with activities of daily living, such as personal care (toilet, feeding, dressing, grooming, ambulation, or bathing), preparing meals, keeping house, providing transportation, and handling finances; these are in addition to medical/nursing tasks and emotional support. Caregivers also locate and coordinate health services and supports, communicate with health providers, make decisions about and implement care plans (Reinhard et al., 2019). The responsibilities of caregiving affect numerous aspects of the caregivers' life including ability to work, engagement in social life, and mental and physical health (Talley & Crews, 2007).

### *Caregiver Health Problems*

Providing care to relatives with chronic illness or disability is understood to be a stressful experience, associated with declines in the caregiver's psychological and physical health. In a national survey, 23% of caregivers reported that caregiving had made their health worse (National Alliance for Caregiving and AARP, 2020). Nearly 40% of caregivers indicated high emotional stress and 17% reported high physical strain as a direct result of their caregiving duties (National Alliance for Caregiving

and AARP, 2020). Caregivers are faced with difficult caregiving tasks, emotional and behavioral problems of the care recipient, and concerns about disease progression (Schulz & Eden, 2016). They also are prone to encounter restrictions of time for personal and social life and for management of their own chronic conditions due to strains from the caregiving role (Dionne-Odom et al., 2017; Lambert et al., 2016). These can lead to a high level of caregiving stress which is associated with poorer health outcomes including mental and physical health, quality of life, and increased mortality compared to non-caregivers (Kim et al., 2015; Perkins et al., 2013; Schulz & Beach, 1999).

### *Cardiovascular Risk in Caregivers*

Increased cardiovascular disease (CVD) risk among caregivers has been documented by a growing body of research (Buyck et al., 2013; Capistrant, Moon, Berkman, et al., 2012; Lee et al., 2003; Miyawaki et al., 2017). Studies have suggested that caregivers are at 1.13 – 2.37 times higher risk of CVD incidence than non-caregivers (Buyck et al., 2013; Capistrant, Moon, Berkman, et al., 2012; Ji et al., 2012) with studies indicating that caregiving predicts higher risks of incident hypertension (Capistrant, Moon, & Glymour, 2012; Torimoto-Sasai et al., 2015) and metabolic syndrome (Kring et al., 2010; Ross et al., 2017). An 8-year longitudinal study with 8,472 spousal caregivers aged 50 years and older showed that caregiving significantly predicted CVD incidence (Hazard Ratio [HR] = 1.35, 95% Confidence Interval [CI] = 1.06-1.68) (Capistrant, Moon, Berkman, et al., 2012). Long-term caregiving, defined as providing informal care at two consecutive biennial surveys, was associated with double the risk of CVD onset (HR = 1.95, 95% CI = 1.19-3.18). In addition, a 20-year longitudinal study with comprehensive Swedish national data found that caregivers whose spouse was diagnosed with cancer during the period had a 13% to 29% higher risk of CVD and stroke, compared with a matched reference group (Ji et al., 2012).

### *Psychological Factors*

A substantial body of literature examining the general population found that people with higher psychological stress are at higher risk of CVD, using a variety of biomarkers (e.g., c-reactive protein, lipoprotein-associated phospholipase, interleukin-6, and catecholamine, flow-mediated dilation, carotid

intima-media thickness, and blood pressure variability) (Kershaw et al., 2017; Steptoe et al., 2007; Wiernik et al., 2016; Winning et al., 2015). For example, one study demonstrated that higher chronic stress was associated with lower absolute flow-mediated dilation, controlling for demographic and socioeconomic characteristics (Kershaw et al., 2017). The accumulated evidence on the adverse impacts of psychological stress on CVD risk suggests that caregiving stress may play a major role in their increased CVD risk.

It has been reported that 30-70% of caregivers experience psychological symptoms (e.g., caregiving stress, anxiety, and depression) (Areia et al., 2019; Steel et al., 2019; Ullrich et al., 2017). Despite evidence of chronic exposure to these stressors being associated with excessive risk of CVD incidence, the relationships between the psychological symptoms and CVD risk among caregivers are not well understood (Cohen et al., 2015; Wirtz & von Kanel, 2017). In an 18-month longitudinal study that followed caregivers without history of CVD who cared for patients with dementia, depressive symptoms and distress of providing care were independent significant predictors of time-to-develop CVD (Mausbach et al., 2007). A small number of studies examined the association between caregiving stress and CVD risk (Aschbacher et al., 2008; Gouin et al., 2012; Haley et al., 2010; Roepke et al., 2012); other researchers assumed that caregiving status alone (i.e., caregivers vs. non-caregivers) represented psychological stress rather than actually measuring stress-related symptoms (Ji et al., 2012; Roepke et al., 2011). To better understand mechanisms in which psychological symptoms affect caregivers' cardiovascular health, caregiving status and psychological distress related to caregiving must be differentiated.

***Sleep as a Behavioral Factor***

Impaired sleep has been found to have unfavorable physiological effects linked to CVD; and poor sleep disturbance has been cited as an independent predictor of CVD incidence (Hoevenaar-Blom et al., 2011; Kwok et al., 2018; Lao et al., 2018). Based on recent investigations of the mechanism, impaired sleep is likely to modify hemodynamic control and autonomic regulation in the cardiovascular system along with inflammatory responses and endothelial dysfunction (Calvin et al., 2014; Irwin et al., 2008;

Tobaldini et al., 2013).

It is quite common for caregivers to encounter sleep problems. Research suggests 32-100% of caregivers report poor sleep quality, and objective measures of sleep features using actigraphy have demonstrated sleep disturbances in caregivers (Chiu et al., 2014; Cupidi et al., 2012; Lee et al., 2015; Morris et al., 2015; von Känel et al., 2010). In a review study including 22 studies on sleep among caregivers, the median sleep duration at night was 7.3 hours (interquartile range [IQR] = 1.4) and the median time staying awake during time intended for sleep was 64 minutes (IQR = 23) (Byun et al., 2016). In a general population-based study, the parameters were 7.8 hours (IQR = 1.6) and 36 minutes (IQR = 24), respectively (Morgan et al., 2017). Although there is a limitation for a direct comparison due to potentially different characteristics among the samples, caregivers appear to experience relatively more sleep disturbance compared with non-caregivers.

Despite the growing evidence of caregivers' vulnerability to sleep problems and the implications of sleep problems for CVD risk, only a few studies have examined the relationship specifically among caregivers. In a study that assessed associations of subjective sleep quality and objectively measured sleep parameters with biomarkers of atherosclerosis, significant relationships of decreased sleep duration with interlukin-6 and c-reactive protein, respectively, were observed in caregivers in contrast to non-caregivers (von Känel et al., 2010). Two other studies investigating the association between caregivers' sleep disturbance and biomarkers also demonstrated that wake after sleep onset was an independent predictor of plasma D-dimer levels, which indicates a procoagulant effect (Mausbach et al., 2006; Mills et al., 2009). However, these studies were limited by a small sample size requiring further validation. Considering caregivers' susceptibility to impaired sleep, further investigations that examine the relationship between sleep characteristics and CVD risk among caregivers are warranted.

***Subclinical Markers***

Much attention has been paid to subclinical CVD markers, such as blood pressure variability (BPV), non-dipping blood pressure, and arterial stiffness, as these are considered fundamental precursors that identify those who are at increased risk for CVD and enable primary CVD prevention (Ambrosino et

al., 2016; Mamudu et al., 2015; Wang et al., 2017; Yao et al., 2018). Recent meta-analysis studies found that BPV (Stevens et al., 2016) and non-dipping blood pressure (Taylor et al., 2015) were independent predictors of CVD (including coronary heart disease, stroke, all cardiovascular events, and all-cause mortality), beyond conventional risk factors among those without preexisting CVD. Increased CVD risk has been attributed to stress-related dysregulation in physiological responses. Prolonged responses to chronic stressors lead the sympatho-adrenal medullary systems and the hypothalamic-pituitary-adrenal axis to be disrupted resulting in neural and humoral dysregulation (Gavrilovic & Dronjak, 2005; Uschold-Schmidt et al., 2013). Subclinical markers represent pre-symptomatic stages of CVD that are chronic conditions caused from the prolonged activation of this stress process, such as autonomic dysregulation and functional/structural changes in the cardiovascular system that may amplify adverse effects on cardiovascular outcomes (Farah et al., 2004; Holt-Lunstad & Steffen, 2007; Kim et al., 2018; Stewart et al., 2003). Despite their prognostic significance as independent risk factors for CVD, subclinical markers have not been widely used to assess CVD risk in the population of caregivers.

***Blood Pressure Variability.*** Among subclinical CVD markers, BPV is considered to have physio-pathological and prognostic importance in addition to average blood pressure values (Mancia, 2012; Parati et al., 2013). Blood pressure oscillates in response to various factors (physiological, behavioral, and environmental) for homeostasis; yet if this physiological fluctuation is excessive, that indicates some alterations in hemodynamic systems or pathological conditions (Rosei et al., 2020). The disturbed baroreflex causes increased BPV which may be one of the mediators in the development of CVD. Especially short-term BPV, which is derived from 24-hour blood pressure measurements, is known to reflect sympathetic activation and arterial compliance (Parati et al., 2020). A large number of studies have shown that short-term BPV predicts CVD incidence and mortality as well as organ damage in the general population and the hypertensive population independent of mean blood pressure (Cremer et al., 2021; Hsu et al., 2016; Saladini et al., 2020; Sander et al., 2000; Stevens et al., 2016). This accumulated evidence suggests that BPV can be utilized in identifying caregivers at high risk of CVD and elucidating underlying mechanism by which caregiving contributes to CVD development.

### *Relationships of Psychological and Behavioral factors with Cardiovascular Risk*

Although psychological symptoms, such as caregiving stress, depression, and anxiety, and impaired sleep are both prevalent in caregivers, and are known to be implicated in cardiovascular health, the relationships among these psychobehavioral factors and CVD risk in the caregiver population have been understudied. Better understanding of the links among risk factors for CVD in caregivers and potential pathways in which caregivers' cardiovascular health may deteriorate can inform future interventions for optimizing early prevention of CVD in caregivers.

## Study Purpose and Specific Aims

The purpose of this cross-sectional study was to investigate the relationships among psychological symptoms, sleep quality, and CVD risk using a subclinical marker in caregivers of patients with chronic illness. Caregivers aged 18 years or older who are providing in-home care to adult patients with chronic illness were recruited from the community. Psychological symptoms (caregiving stress, depression, and anxiety) were assessed by questionnaires, and objective sleep quality including sleep efficiency, wake after sleep onset, and the number of awakenings was measured using actigraphy. CVD risk was operationalized by short-term BPV. Potential confounding factors included age, sex, race/ethnicity, smoking, sleep apnea or diabetes diagnosis, antihypertensive or cholesterol medication use, body mass index, and mean arterial pressure.

The specific aims of this study are: (1) To assess the dynamics and patterns of sleep quality status by the levels of psychological symptoms; (2) To examine the associations of psychological symptoms and objective sleep quality with short-term BPV.

## Conceptual Framework

This study was underpinned by a conceptual framework that adapted the concept of allostasis and allostatic load (Figure 1) (McEwen & Stellar, 1993). Allostasis is a dynamic system that recognizes and responds to stressors, and promotes recovery (McEwen, 1998). The system maintains a physiological balance through neuroendocrine responses that regulate metabolic, immune, and cardiovascular systems. However, when allostatic challenges such as environmental demands and chronic stressors are too great,

the systems can be dysregulated through psychological, behavioral, and physiological reactions and produce allostatic load leading to damaging outcomes, such as cardiovascular and metabolic diseases (Edes & Crews, 2017). In this study, caregiving demands represent chronic stressors that could cause allostatic challenges. Psychological factors were operationalized by levels of caregiving stress, depression, and anxiety; behavioral reactions by objectively measured sleep quality; and physiological reactions by short-term BPV as a proxy for the cardiovascular change of allostatic response (Figure 2).

## References

Ambrosino, P., Lupoli, R., Tortora, A., Cacciapuoti, M., Lupoli, G. A., Tarantino, P., Nasto, A., & Di Minno, M. N. D. (2016). Cardiovascular risk markers in patients with primary aldosteronism: A systematic review and meta-analysis of literature studies. *International Journal of Cardiology*, *208*, 46–55. https://doi.org/10.1016/j.ijcard.2016.01.200

Areia, N. P., Fonseca, G., Major, S., & Relvas, A. P. (2019). Psychological morbidity in family caregivers of people living with terminal cancer: Prevalence and predictors. *Palliative and Supportive Care*, *17*(3), 286–293. https://doi.org/10.1017/S1478951518000044

Aschbacher, K., Mills, P. J., Känel, R. von, Hong, S., Mausbach, B. T., Roepke, S. K., Dimsdale, J. E., Patterson, T. L., Ziegler, M. G., Ancoli-Israel, S., & Grant, I. (2008). Effects of depressive and anxious symptoms on norepinephrine and platelet P-selectin responses to acute psychological stress among elderly caregivers. *Brain, Behavior, and Immunity*, *22*(4), 493–502. https://doi.org/10.1016/J.BBI.2007.10.002

Buyck, J. F., Ankri, J., Dugravot, A., Bonnaud, S., Nabi, H., Kivimaki, M., & Singh-Manoux, A. (2013). Informal caregiving and the risk for coronary heart disease: The Whitehall II study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *68*(10), 1316–1323. https://doi.org/10.1093/gerona/glt025

Byun, E., Lerdal, A., Gay, C. L., & Lee, K. A. (2016). How adult caregiving impacts sleep: A systematic review. *Current Sleep Medicine Reports*, *2*(4), 191–205. https://doi.org/10.1007/s40675-016-0058-8

Calvin, A. D., Covassin, N., Kremers, W. K., Adachi, T., Macedo, P., Albuquerque, F. N., Bukartyk, J., Davison, D. E., Levine, J. A., Singh, P., Wang, S., & Somers, V. K. (2014). Experimental sleep restriction causes endothelial dysfunction in healthy humans. *Journal of the American Heart Association*, *3*(6), e001143. https://doi.org/10.1161/JAHA.114.001143

Capistrant, B. D., Moon, J. R., Berkman, L. F., & Glymour, M. M. (2012). Current and long-term spousal caregiving and onset of cardiovascular disease. *Journal of Epidemiology and Community Health*,

*66*(10), 951–956. https://doi.org/10.1136/jech-2011-200040

Capistrant, B. D., Moon, J. R., & Glymour, M. M. (2012). Spousal caregiving and incident hypertension. *American Journal of Hypertension*, *25*(4), 437–443. https://doi.org/10.1038/ajh.2011.232

Chiu, Y. C., Lee, Y. N., Wang, P. C., Chang, T. H., Li, C. L., Hsu, W. C., & Lee, S. H. (2014). Family caregivers' sleep disturbance and its associations with multilevel stressors when caring for patients with dementia. *Aging & Mental Health*, *18*(1), 92–101. https://doi.org/10.1080/13607863.2013.837141

Cohen, B. E., Edmondson, D., & Kronish, I. M. (2015). State of the art review: Depression, stress, anxiety, and cardiovascular disease. *American Journal of Hypertension*, *28*(11), 1295–1302. https://doi.org/10.1093/ajh/hpv047

Cremer, A., Doublet, J., Boulestreau, R., Gaudissard, J., Tzourio, C., & Gosse, P. (2021). Short-term blood pressure variability, arterial stiffness, and cardiovascular events: Results from the Bordeaux cohort. *Journal of Hypertension*, *39*(5), 947–951. https://doi.org/10.1097/HJH.0000000000002735

Cupidi, C., Realmuto, S., Lo Coco, G., Cinturino, A., Talamanca, S., Arnao, V., Perini, V., Piccoli, T., D'Amelio, M., Savettieri, G., & Lo Coco, D. (2012). Sleep quality in caregivers of patients with Alzheimer's disease and Parkinson's disease and its relationship to quality of life. *International Psychogeriatrics*, *24*(11), 1827–1835. https://doi.org/10.1017/S1041610212001032

Dionne-Odom, J. N., Demark-Wahnefried, W., Taylor, R. A., Rocque, G. B., Azuero, A., Acemgil, A., Martin, M. Y., Astin, M., Ejem, D., Kvale, E., Heaton, K., Pisu, M., Partridge, E. E., & Bakitas, M. A. (2017). The self-care practices of family caregivers of persons with poor prognosis cancer: Differences by varying levels of caregiver well-being and preparedness. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, *25*(8), 2437–2444. https://doi.org/10.1007/s00520-017-3650-7

Edes, A. N., & Crews, D. E. (2017). Allostatic load and biological anthropology. *American Journal of Physical Anthropology*, *162*(S63), 44–70. https://doi.org/10.1002/ajpa.23146

Farah, V. M. A., Joaquim, L. F., Bernatova, I., & Morris, M. (2004). Acute and chronic stress influence

blood pressure variability in mice. *Physiology and Behavior*, *83*(1 SPEC. ISS.), 135–142. https://doi.org/10.1016/j.physbeh.2004.08.004

Gavrilovic, L., & Dronjak, S. (2005). Activation of rat pituitary-adrenocortical and sympatho-adrenomedullary system in response to different stressors. *Neuro Endocrinology Letters*, *26*(5), 515–520. http://www.ncbi.nlm.nih.gov/pubmed/16264408

Gouin, J. P., Glaser, R., Malarkey, W. B., Beversdorf, D., & Kiecolt-Glaser, J. (2012). Chronic stress, daily stressors, and circulating inflammatory markers. *Health Psychology*, *31*(2), 264–268. https://doi.org/10.1037/a0025536

Haley, W. E., Roth, D. L., Howard, G., & Safford, M. M. (2010). Caregiving strain and estimated risk for stroke and coronary heart disease among spouse caregivers differential effects by race and sex. *Stroke*, *41*(2), 331–336. https://doi.org/10.1161/STROKEAHA.109.568279

Hoevenaar-Blom, M. P., Spijkerman, A. M. W., Kromhout, D., Van Den Berg, J. F., & Verschuren, W. M. M. (2011). Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: The MORGEN study. *Sleep*, *34*(11), 1487–1492. https://doi.org/10.5665/sleep.1382

Holt-Lunstad, J., & Steffen, P. R. (2007). Diurnal cortisol variation is associated with nocturnal blood pressure dipping. *Psychosomatic Medicine*, *69*(4), 339–343. https://doi.org/10.1097/PSY.0b013e318050d6cc

Hsu, P. F., Cheng, H. M., Wu, C. H., Sung, S. H., Chuang, S. Y., Lakatta, E. G., Yin, F. C. P., Chou, P., & Chen, C. H. (2016). High short-term blood pressure variability predicts long-term cardiovascular mortality in untreated hypertensives but not in normotensives. *American Journal of Hypertension*, *29*(7), 806–813. https://doi.org/10.1093/AJH/HPW002

Irwin, M. R., Wang, M., Ribeiro, D., Cho, H. J., Olmstead, R., Breen, E. C., Martinez-Maza, O., & Cole, S. (2008). Sleep loss activates cellular inflammatory signaling. *Biological Psychiatry*, *64*(6), 538–540. https://doi.org/10.1016/j.biopsych.2008.05.004

Ji, J., Zoller, B., Sundquist, K., & Sundquist, J. (2012). Increased risks of coronary heart disease and stroke

among spousal caregivers of cancer patients. *Circulation*, *125*(14), 1742–1747. https://doi.org/10.1161/CIRCULATIONAHA.111.057018

Kershaw, K. N., Lane-Cordova, A. D., Carnethon, M. R., Tindle, H. A., & Liu, K. (2017). Chronic stress and endothelial dysfunction: The Multi-Ethnic Study of Atherosclerosis (MESA). *American Journal of Hypertension*, *30*(1), 75–80. https://doi.org/10.1093/ajh/hpw103

Kim, H. G., Cheon, E. J., Bai, D. S., Lee, Y. H., & Koo, B. H. (2018). Stress and heart rate variability: A meta-analysis and review of the literature. *Psychiatry Investigation*, *15*(3), 235–245. https://doi.org/10.30773/pi.2017.08.17

Kim, Y., Carver, C., Shaffer, K., Gansler, T., & Cannady, R. (2015). Cancer caregiving predicts physical impairments: Roles of earlier caregiving stress and being a spousal caregiver. *Cancer*, *121*(2), 302–310. https://doi.org/10.1002/cncr.29040

Kring, S. I. I., Brummett, B. H., Barefoot, J., Garrett, M. E., Ashley-Koch, A. E., Boyle, S. H., Siegler, I. C., Sorensen, T. I. A., & Williams, R. B. (2010). Impact of psychological stress on the associations between apolipoprotein E variants and metabolic traits: Findings in an American sample of caregivers and controls. *Psychosomatic Medicine*, *72*(5), 427–433. https://doi.org/10.1097/PSY.0b013e3181de30ad

Kwok, C. S., Kontopantelis, E., Kuligowski, G., Gray, M., Muhyaldeen, A., Gale, C. P., Peat, G. M., Cleator, J., Chew-Graham, C., Loke, Y. K., & Mamas, M. A. (2018). Self-reported sleep duration and quality and cardiovascular disease and mortality: A dose-response meta-analysis. *Journal of the American Heart Association*, *7*(15). https://doi.org/10.1161/JAHA.118.008552

Lambert, S. D., Levesque, J. V., & Girgis, A. (2016). The impact of cancer and chronic conditions on caregivers and family members. In *Cancer and Chronic Conditions* (pp. 159–202). Springer Singapore. https://doi.org/10.1007/978-981-10-1844-2_6

Lao, X. Q., Liu, X., Deng, H. B., Chan, T. C., Ho, K. F., Wang, F., Vermeulen, R., Tam, T., Wong, M. C. S., Tse, L. A., Chang, L. Y., & Yeoh, E. K. (2018). Sleep quality, sleep duration, and the risk of

coronary heart disease: A prospective cohort study with 60, 586 adults. *Journal of Clinical Sleep Medicine*, *14*(1), 109–117. https://doi.org/10.5664/jcsm.6894

Lee, K. C., Yiin, J. J., Lin, P. C., & Lu, S. H. (2015). Sleep disturbances and related factors among family caregivers of patients with advanced cancer. *Psycho-Oncology*, *24*(12), 1632–1638. https://doi.org/10.1002/pon.3816

Lee, S., Colditz, G. A., Berkman, L. F., & Kawachi, I. (2003). Caregiving and risk of coronary heart disease in U.S. women: A prospective study. *American Journal of Preventive Medicine*, *24*(2), 113–119. https://doi.org/10.1016/s0749-3797(02)00582-2

Mamudu, H. M., Paul, T., Veeranki, S. P., Wang, L., Panchal, H. B., & Budoff, M. (2015). Subclinical atherosclerosis and relationship with risk factors of coronary artery disease in a rural population. *The American Journal of the Medical Sciences*, *350*(4), 257–262. https://doi.org/10.1097/MAJ.0000000000000548

Mancia, G. (2012). Short- and long-term blood rressure variability. *Hypertension*, *60*(2), 512–517. https://doi.org/10.1161/HYPERTENSIONAHA.112.194340

Mausbach, B. T., Ancoli-Israel, S., von Kanel, R., Patterson, T. L., Aschbacher, K., Mills, P. J., Ziegler, M. G., Dimsdale, J. E., Calleran, S., & Grant, I. (2006). Sleep disturbance, norepinephrine, and D-dimer are all related in elderly caregivers of people with Alzheimer disease. *Sleep*, *29*(10), 1347–1352.

Mausbach, B. T., Patterson, T. L., Rabinowitz, Y. G., Grant, I., & Schulz, R. (2007). Depression and distress predict time to cardiovascular disease in dementia caregivers. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *26*(5), 539–544. https://doi.org/10.1037/0278-6133.26.5.539

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*(1), 33–44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

McEwen, B. S., & Stellar, E. (1993). Stress and the individual. *Archives of Internal Medicine*, *153*(18), 2093. https://doi.org/10.1001/archinte.1993.00410180039004

Mills, P. J., Ancoli-Israel, S., von Kanel, R., Mausbach, B. T., Aschbacher, K., Patterson, T. L., Ziegler, M. G., Dimsdale, J. E., & Grant, I. (2009). Effects of gender and dementia severity on Alzheimer's disease caregivers' sleep and biomarkers of coagulation and inflammation. *Brain, Behavior, and Immunity*, *23*(5), 605–610. https://doi.org/10.1016/j.bbi.2008.09.014

Miyawaki, A., Tomio, J., Kobayashi, Y., Takahashi, H., Noguchi, H., & Tamiya, N. (2017). Impact of long-hours family caregiving on non-fatal coronary heart disease risk in middle-aged people: Results from a longitudinal nationwide survey in Japan. *Geriatrics and Gerontology International*, *17*(11), 2109–2115. https://doi.org/10.1111/ggi.13061

Morgan, E., Schumm, L. P., McClintock, M., Waite, L., & Lauderdale, D. S. (2017). Sleep characteristics and daytime cortisol levels in older adults. *Sleep*, *40*(5). https://doi.org/10.1093/sleep/zsx043

Morris, B. A., Thorndike, F. P., Ritterband, L. M., Glozier, N., Dunn, J., & Chambers, S. K. (2015). Sleep disturbance in cancer patients and caregivers who contact telephone-based help services. *Supportive Care in Cancer*, *23*(4), 1113–1120. https://doi.org/10.1007/s00520-014-2458-y

National Alliance for Caregiving and AARP. (2020). *Caregiving in the U.S. 2020 - AARP Research Report*. https://www.caregiving.org/caregiving-in-the-us-2020/

Parati, G., Ochoa, J. E., Lombardi, C., & Bilo, G. (2013). Assessment and management of blood-pressure variability. *Nature Reviews Cardiology*, *10*(3), 143–155. https://doi.org/10.1038/nrcardio.2013.1

Parati, G., Torlasco, C., Pengo, M., Bilo, G., & Ochoa, J. E. (2020). Blood pressure variability: Its relevance for cardiovascular homeostasis and cardiovascular diseases. *Hypertension Research : Official Journal of the Japanese Society of Hypertension*, *43*(7), 609–620. https://doi.org/10.1038/s41440-020-0421-5

Perkins, M., Howard, V. J., Wadley, V. G., Crowe, M., Safford, M. M., Haley, W. E., Howard, G., & Roth, D. L. (2013). Caregiving strain and all-cause mortality: Evidence from the REGARDS study. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *68*(4), 504–512. https://doi.org/10.1093/geronb/gbs084

Reinhard, S. C., Feinberg, L. F., Houser, A., Choula, R., & Evans, M. (2019). *Valuing the Invaluable: 2019*

*Update - AARP Insight on the Issues*. https://www.aarp.org/content/dam/aarp/ppi/2019/11/valuing-the-invaluable-2019-update-charting-a-path-forward.doi.10.26419-2Fppi.00082.001.pdf

Roepke, S., Allison, M., Von Kanel, R., Mausbach, B., Chattillion, E., Harmell, A., Patterson, T., Dimsdale, J., Mills, P., Ziegler, M., Ancoli-Israel, S., & Grant, I. (2012). Relationship between chronic stress and carotid intima-media thickness (IMT) in elderly Alzheimer's disease caregivers. *Stress (Amsterdam, Netherlands)*, *15*(2), 121–129. https://doi.org/10.3109/10253890.2011.596866

Roepke, S., Mausbach, B., Patterson, T., Von Känel, R., Ancoli-Israel, S., Harmell, A., Dimsdale, J., Aschbacher, K., Mills, P., Ziegler, M., Allison, M., & Grant, I. (2011). Effects of Alzheimer caregiving on allostatic load. *Journal of Health Psychology*, *16*(1), 58–69. https://doi.org/10.1177/1359105310369188

Rosei, E. A., Chiarini, G., & Rizzoni, D. (2020). How important is blood pressure variability? *European Heart Journal Supplements: Journal of the European Society of Cardiology*, *22*(Suppl E), E1–E6. https://doi.org/10.1093/eurheartj/suaa061

Ross, A., Shamburek, R., Wehrlen, L., Klagholz, S. D., Yang, L., Stoops, E., Flynn, S. L., Remaley, A. T., Pacak, K., Shelburne, N., & Bevans, M. F. (2017). Cardiometabolic risk factors and health behaviors in family caregivers. *PloS One*, *12*(5), e0176408–e0176408. https://doi.org/10.1371/journal.pone.0176408

Saladini, F., Fania, C., Mos, L., Vriz, O., Mazzer, A., Spinella, P., Garavelli, G., Ermolao, A., Rattazzi, M., & Palatini, P. (2020). Short-term but not long-term blood pressure variability is a predictor of adverse cardiovascular outcomes in young untreated hypertensives. *American Journal of Hypertension*, *33*(11), 1030–1037. https://doi.org/10.1093/ajh/hpaa121

Sander, D., Kukla, C., Klingelhöfer, J., Winbeck, K., & Conrad, B. (2000). Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis. *Circulation*, *102*(13), 1536–1541. https://doi.org/10.1161/01.CIR.102.13.1536

Schulz, R, & Beach, S. R. (1999). Caregiving as a risk factor for mortality: The Caregiver Health Effects

Study. *JAMA*, *282*(23), 2215–2219.

Schulz, R., Eden, J., Committee on Family Caregiving for Older Adults, Board on Health Care Services, Health and Medicine Division, & National Academies of Sciences, Engineering, and Medicine (Eds.). (2016). *Families Caring for an Aging America*. National Academies Press (US). https://doi.org/10.17226/23606

Steel, J. L., Cheng, H., Pathak, R., Wang, Y., Miceli, J., Hecht, C. L., Haggerty, D., Peddada, S., Geller, D. A., Marsh, W., Antoni, M., Jones, R., Kamarck, T., & Tsung, A. (2019). Psychosocial and behavioral pathways of metabolic syndrome in cancer caregivers. *Psycho-Oncology*. https://doi.org/10.1002/pon.5147

Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity*, *21*(7), 901–912. https://doi.org/10.1016/j.bbi.2007.03.011

Stevens, S. L., Wood, S., Koshiaris, C., Law, K., Glasziou, P., Stevens, R. J., & McManus, R. J. (2016). Blood pressure variability and cardiovascular disease: Systematic review and meta-analysis. *BMJ (Clinical Research Ed.)*, *354*, i4098. https://doi.org/10.1136/bmj.i4098

Stewart, A. D., Millasseau, S. C., Kearney, M. T., Ritter, J. M., & Chowienczyk, P. J. (2003). Effects of inhibition of basal nitric oxide synthesis on carotid-femoral pulse wave velocity and augmentation index in humans. *Hypertension*, *42*(5), 915–918. https://doi.org/10.1161/01.HYP.0000092882.65699.19

Talley, R. C., & Crews, J. E. (2007). Framing the public health of caregiving. *American Journal of Public Health*, *97*(2), 224–228. https://doi.org/10.2105/AJPH.2004.059337

Taylor, K. S., Heneghan, C. J., Stevens, R. J., Adams, E. C., Nunan, D., & Ward, A. (2015). Heterogeneity of prognostic studies of 24-hour blood pressure variability: Systematic review and meta-analysis. *PLOS ONE*, *10*(5), e0126375. https://doi.org/10.1371/journal.pone.0126375

Tobaldini, E., Cogliati, C., Fiorelli, E. M., Nunziata, V., Wu, M. A., Prado, M., Bevilacqua, M., Trabattoni,

D., Porta, A., & Montano, N. (2013). One night on-call: Sleep deprivation affects cardiac autonomic control and inflammation in physicians. *European Journal of Internal Medicine*, *24*(7), 664–670. https://doi.org/10.1016/j.ejim.2013.03.011

Torimoto-Sasai, Y., Igarashi, A., Wada, T., Ogata, Y., & Yamamoto-Mitani, N. (2015). Female family caregivers face a higher risk of hypertension and lowered estimated glomerular filtration rates: A cross-sectional, comparative study. *BMC Public Health*, *15*, 177. https://doi.org/10.1186/s12889-015-1519-6

Ullrich, A., Ascherfeld, L., Marx, G., Bokemeyer, C., Bergelt, C., & Oechsle, K. (2017). Quality of life, psychological burden, needs, and satisfaction during specialized inpatient palliative care in family caregivers of advanced cancer patients. *BMC Palliative Care*, *16*(1), 31. https://doi.org/10.1186/s12904-017-0206-z

Uschold-Schmidt, N., Peterlik, D., Füchsl, A. M., & Reber, S. O. (2013). HPA axis changes during the initial phase of psychosocial stressor exposure in male mice. *The Journal of endocrinology*, *218*(2), 193–203. https://doi.org/10.1530/JOE-13-0027

von Känel, R., Ancoli-Israel, S., Dimsdale, J. E., Mills, P. J., Mausbach, B. T., Ziegler, M. G., Patterson, T. L., Grant, I., von Kanel, R., Ancoli-Israel, S., Dimsdale, J. E., Mills, P. J., Mausbach, B. T., Ziegler, M. G., Patterson, T. L., & Grant, I. (2010). Sleep and biomarkers of atherosclerosis in elderly Alzheimer caregivers and controls. *Gerontology*, *56*(1), 41–50. https://doi.org/10.1159/000264654

Wang, Y. Q., Wang, C. F., Zhu, L., Yuan, H., Wu, L. X., & Chen, Z. H. (2017). Ideal cardiovascular health and the subclinical impairments of cardiovascular diseases: A cross-sectional study in central south China. *BMC Cardiovascular Disorders*, *17*(1), 269. https://doi.org/10.1186/s12872-017-0697-9

Wiernik, E., Lemogne, C., Thomas, F., Perier, M.-C., Guibout, C., Nabi, H., Laurent, S., Pannier, B., Boutouyrie, P., Jouven, X., & Empana, J. P. (2016). Perceived stress, common carotid intima media thickness and occupational status: The Paris Prospective Study III. *International Journal of Cardiology*, *221*, 1025–1030. https://doi.org/10.1016/j.ijcard.2016.07.068

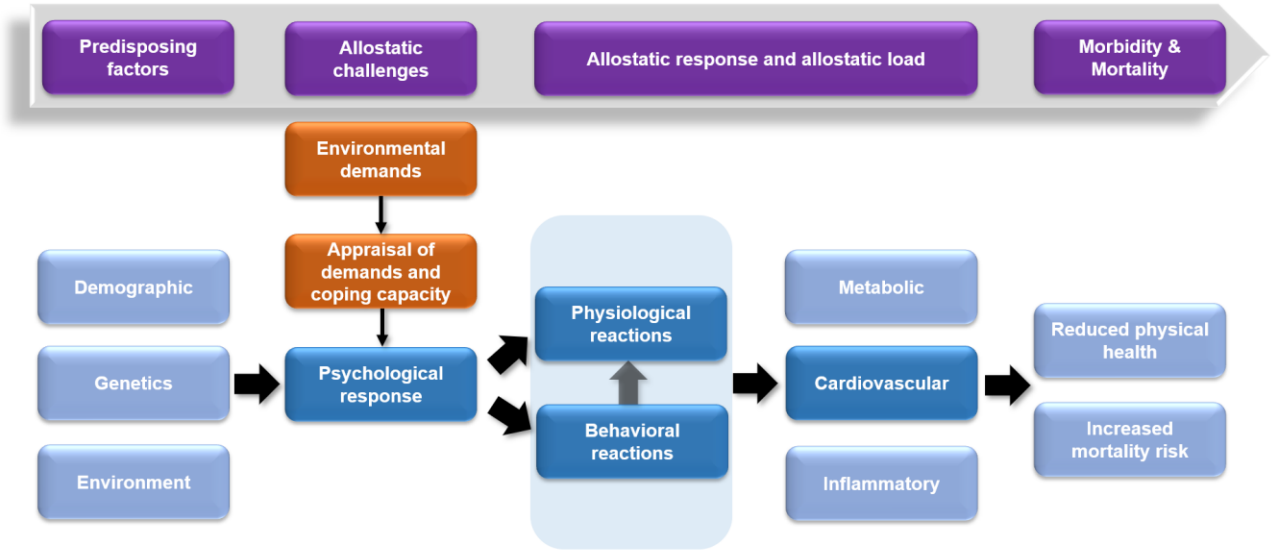
Winning, A., Glymour, M. M., McCormick, M. C., Gilsanz, P., & Kubzansky, L. D. (2015). Psychological distress across the life course and cardiometabolic risk: Findings from the 1958 British Birth Cohort Study. *Journal of the American College of Cardiology*, *66*(14), 1577–1586. https://doi.org/10.1016/j.jacc.2015.08.021

Wirtz, P. H., & von Kanel, R. (2017). Psychological stress, inflammation, and coronary heart disease. *Current Cardiology Reports*, *19*(11), 111. https://doi.org/10.1007/s11886-017-0919-x

Yao, K., Zhao, T., Zeng, L., Yang, J., Liu, Y., He, Q., & Zou, X. (2018). Non-invasive markers of cardiovascular risk in patients with subclinical hypothyroidism: A systematic review and meta-analysis of 27 case control studies. *Scientific Reports*, *8*(1), 4579. https://doi.org/10.1038/s41598-018-22897-3

**Figure 1**

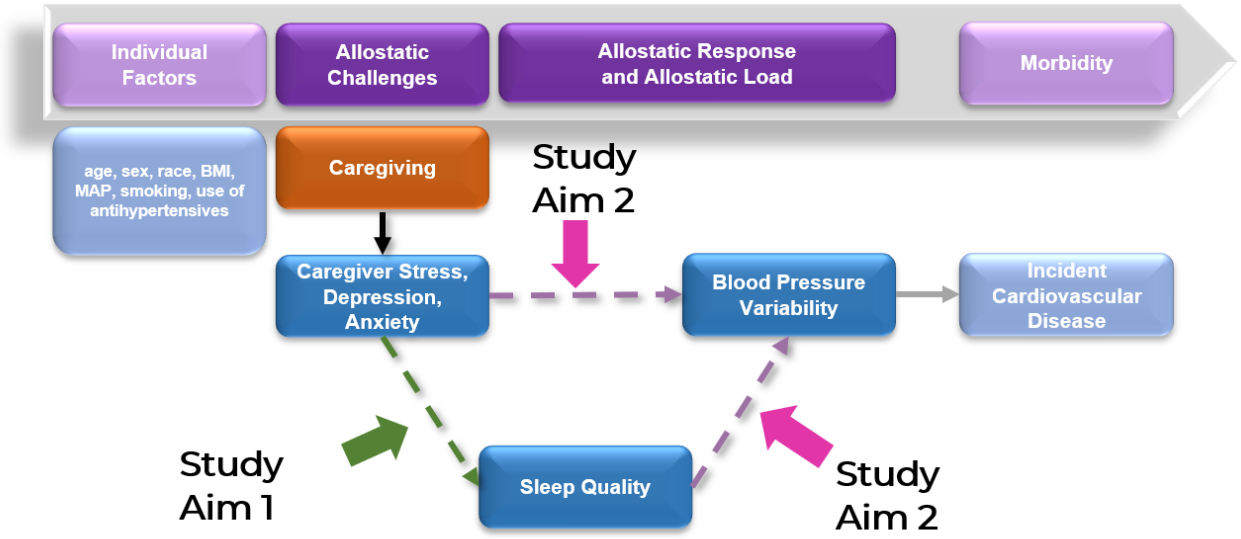
*Allostasis and Allostatic Load*




*Note.* Adapted from McEwen B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44; and Edes, A. N., & Crews, D. E. (2017). Allostatic load and biological anthropology. *American journal of physical anthropology*, *162 Suppl 63*, 44–70.

**Figure 2**

*Conceptual Framework of the Study*



# Chapter 2: Methodology

## Study Design

This study employed a descriptive, correlational, and cross-sectional study to examine relationships among psychological symptoms, sleep, and CVD risk in a sample of caregivers providing in-home care for patients with chronic illness. The independent variables in this study were caregiving stress, depression, anxiety, and objectively measured sleep quality which would be examined whether they are associated with the dependent variable, short-term blood pressure variability (BPV).

## Subjects and Setting

A convenience sample of adult caregivers aged 18 years or older was recruited from Charlottesville, Virginia and its surrounding areas. Inclusion criteria were caregivers who (1) are primarily responsible for providing in-home care and personal assistance to an adult family member or friend with chronic illness; and (2) have no major health conditions such as cancer and cardiac conditions. Exclusion criteria included (1) professional caregivers to the care-recipients; (2) caregivers of patients admitted in hospitals, nursing skilled facilities, or nursing homes; and (3) night-shift workers.

## Measures

Data of individual characteristics (age, sex, race/ethnicity, smoking, diagnosis of sleep apnea or diabetes, use of antihypertensive or cholesterol medications, general health status, body mass index, and mean arterial pressure) and caregiving characteristics (care recipient's heath conditions, relationships, caregiving hours and duration) were collected. Also, psychological symptoms (caregiving stress, depression, and anxiety), sleep quality, and short-term BPV were measured (Table 1).

### *Individual Characteristics*

Age, sex, race/ethnicity, smoking (current, past, or never smoker), diagnosis of sleep apnea or diabetes, and use of antihypertensive or cholesterol medications, and general health status (excellent, very good, good, fair, or poor) were self-reported. Body mass index was be calculated using height and weight measured by an Accu-Hite wall mounted stadiometer (WA, US) and a Withings electronic scale (PA, US), respectively. Office blood pressure (BP) was measured using Omron 3 Series Upper Arm Blood

Pressure Monitor (Omron, Japan). Measurement of BP followed Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines (Leung et al., 2016). The mid-section circumference of the upper arm was measured with a tape, and the proper sized cuff was selected according to the upper arm circumference. The bladder width was close to 40% of arm circumference and bladder length covered 80-100% of arm circumference. The cuff was applied to the non-dominant arm, and it was placed over the bare arm to maximize reliability of the measures. The artery marker on the cuff was placed over the brachial artery and the cuff was applied snuggly allowing no more than two fingers underneath. After the participants rested comfortably for 10 minutes in the supine position, the arm was kept at the level of the heart without movement and the participants were not spoken to and were asked not to speak during the BP measurement. Using the automated BP monitoring device, BP was measured twice with 2 minutes rest between measures. The mean BP value was recorded as an office BP, and mean arterial pressure was calculated (i.e., mean arterial pressure = [systolic BP + (2 x diastolic BP)] / 3).

***Caregiving Characteristics***

Care recipient's health conditions, the relationship with the care recipient, caregiving hours per week, and caregiving duration were self-reported. Caregivers reported care recipient's health conditions that needed care for, including cancer, dementia or Alzheimer's disease, aging/aging-related health issues, cardiovascular, pulmonary, liver, kidney, cerebrovascular, neurological, orthopedic/musculoskeletal disease, or other. The health conditions were summed. The relationship with the care recipient included spouse, adult child, parent, another family member, and friend or other non-relative.

***Psychological Factors***

Caregiving stress was assessed using the 22-item Zarit Burden Interview (ZBI), a widely used instrument for measuring the level of caregiving stress experienced by the principal caregivers of adult patients (Zarit et al., 1980). The questions focus on major areas such as caregiver's health, psychological well-being, finances, social life, and the relationship between the caregiver and the patient. The 22 items are assessed on a 5-point Likert scale, ranging from 0 = 'never' to 4 = 'nearly always', and scores are added up to give a total score ranging from 0 to 88, with higher scores indicating greater caregiving stress.

The ZBI scale has shown good internal consistency (Cronbach's $\alpha = 0.93$), the intra-class correlation coefficient for the test-rest reliability ($r = 0.89$), and construct validity (Al-Rawashdeh et al., 2016; Schreiner et al., 2006; Seng et al., 2010).

Depression was measured using the Patient Health Questionnaire (PHQ)-9. The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression (Kroenke et al., 2001). The scale scores each of the nine DSM-IV criteria as 0 = 'not at all' to 3 = 'nearly every day'. It has been validated for use in various settings including primary care (Cameron et al., 2008). Good internal consistency has been reported with Cronbach's α ranging from 0.85-0.89 and the intra-class correlation coefficient for the test-rest reliability coefficient ($r = 0.92$) (Gelaye et al., 2013; Kroenke et al., 2001).

Anxiety was measured using Generalized Anxiety Disorder (GAD)-7. The GAD-7 is a seven-item instrument that is used to assess the severity of generalized anxiety disorder (Spitzer et al., 2006). Each item asks the individual to rate the severity of their symptoms over the past two weeks. Response options include 0 = 'not at all', 1 = 'several days', 2 = 'more than half the days', and 3 = 'nearly every day'. The instrument has been validated for primary care patients and general population (Löwe et al., 2008; Mossman et al., 2017; Ruiz et al., 2011). Research has indicated the GAD-7 shows high internal consistency with Cronbach α ranging 0.89-0.92 (Löwe et al., 2008; Spitzer et al., 2006).

***Sleep Quality***

Objective sleep quality was assessed with actigraphy. Actigraphy has been compared against polysomnography (the gold standard for assessing sleep) and has been shown to be reliable and valid (Mantua et al., 2016; Marino et al., 2013). The ActiGraph GT9X Link (ActiGraph; Pensacola, FL, USA) was worn on the non-dominant wrist for 7 consecutive days. The device contains a 3-axis accelerometer with a dynamic range of +/- 8G, and acceleration data are sampled by a 12-bit analog to digital converter at user specified rates ranging from 30 Hz to 100 Hz and stored in a raw, non-filtered/accumulated in the units of gravity (G's). Calculating wrist activity over time allows for an objective measure of duration and disruption of sleep. The recorded actigraphy data were analyzed using the ActiLife software (ActiLife,

Version 6.13.4; Pensacola, FL, USA). Sleep diaries completed by participants were used to validate times the actigraphy watch was removed, bedtimes, and wake times. Sleep quality parameters that were assessed included: (1) sleep efficiency defined as the ratio of the number of sleep minutes (sleep duration) to the total number of minutes spent in bed; (2) wake after sleep onset defined as the total number of minutes that the participant was awake after sleep onset occurred; and (3) frequency of awakenings defined as the number of awakening episodes between the sleep onset and sleep offset.

***Short-term Blood Pressure Variability***

Short-term BPV was assessed using 24-hour ambulatory BP monitoring. Ambulatory BP was recorded for a 24-hour period at 1-hour intervals by means of a validated BP measurement device (Spacelabs 90227; SpaceLabs Healthcare, Washington, USA). Appropriate cuff sizes for the participants' upper arms were used according to the American Heart Association guidelines for BP measurement (Muntner et al., 2019). The arm cuff was positioned on the non-dominant side. The participants were instructed to maintain their normal daily activities but keep the arm extended and immobile at the time of cuff inflation. Recorded readings of BP were downloaded from the monitor into the custom software (Sentinel 11, SpaceLabs Healthcare, Washington, USA). Daytime (awake) and night-time (sleep) intervals were defined individually based on participants' sleep diaries. Recordings that included at least 70% of valid readings per participant throughout the 24-hour period were considered sufficient quality and included in the analysis (O'Brien et al., 2014). As an index of short-term BPV, we computed successive variation (SV) for 24-hour, awake time, and sleep time (Schächinger et al., 1989). The SV accounts for the average of the squared difference between consecutive BP measurements. Compared to the index of standard deviation and coefficient of variation, the SV addresses the time sequence of measurements (Yong et al., 2005) and removes the influence from the superimposed circadian BP variation (Östergren & Isaksson, 1993). The parameter is calculated using the following formula where *n* denotes the number of valid BP readings and *k* is the order of readings:

$$SV = \sqrt{(1/(n-1)\ \sum_{k=1}^{n-1}(BP_{k+1} - BP_k)^2}.$$

**Procedures**

Participants learned about the study via (1) study flyers posted at the University of Virginia (UVA) Health Center and on its clinical trial website, (2) study advertisement in a local newspaper, (3) study information shared in local caregiver support groups, and (4) word of mouth. Interested participants were informed of the study aims and procedures involved over the phone and prescreened for their eligibility. Eligible participants were scheduled for their study visits to a research lab at the UVA School of Nursing. All participants were asked to select a week for study participation that would be representative of their daily life in terms of activities and caregiving tasks. To minimize the variation confounded by circadian patterns of cardiovascular parameters, all study visits were scheduled for the same period of the day (i.e., in the morning between 8am and 11am). Also, participants were asked to refrain from consuming coffee, smoking, eating, and vigorous exercise for at least 3 hours and drinking alcohol for 10 hours before data collection (Laurent et al., 2006).

At the study visit, participants were informed of the research aims, procedure (methods and estimated time to complete), potential benefits and risk in greater detail, and the informed consent was obtained. After obtaining informed consent, participants were asked to complete questionnaires including individual and caregiving characteristics, and psychological symptoms. After completing the questionnaires, participants' height and weight were measured. Next, participants took a rest at least 10 minutes in the supine position before their BP was measured twice with 2 minutes rest between the measurements. Then, an actigraphy device was applied to the non-dominant wrist and worn for 7 consecutive days, and the participants were instructed in how to complete a sleep diary. An ambulatory blood pressure monitor was also applied with a cuff worn on the non-dominant arm, and the participants were instructed in how to terminate the measurement in 24 hours. The devices and completed sleep diary were returned in a week after data collection completion. Each participant received monetary compensation ($60) at the completion of study participation.

**Data Management and Analysis**

Prior to statistical analyses, descriptive statistics for variables of interest and participant

characteristics were performed. Continuous variables were examined for normality, and log transformation was conducted, if needed. Data were tested for violations of assumptions (i.e., normality, linearity, homoscedasticity, and absence of multicollinearity). For the analyses, the level of significance was $\alpha = 0.05$, and the two-tailed tests were used. Statistical analyses were conducted using the RStudio (RStudio Team, 2020) and IBM SPSS Statistics (Version 26) predictive analytic software. Hypotheses for each specific aim and statistical analyses are as follows:

**Specific Aim 1 (Manuscript 2):** To assess the dynamics and patterns of sleep quality status by the levels of psychological symptoms in caregivers.

**Hypothesis:** Caregivers with higher levels of psychological symptoms (caregiving stress, depression, and anxiety) are less likely to transition toward and maintain optimal sleep efficiency state.

**Analysis**: Markov chain transition matrices for groups stratified by each psychological symptom were developed, and short- and long-term patterns of sleep efficiency were estimated.

**Specific Aim 2 (Manuscript 3):** To examine the associations of psychological symptoms and objective sleep quality with short-term BPV in caregivers.

**Hypothesis 1:** Higher psychological symptoms (caregiving stress, depression) are associated with higher BPV.

**Hypothesis 2:** Worse sleep quality (lower sleep efficiency, longer wake after sleep onset, greater number of awakenings) are associated with higher BPV.

**Analysis:** Multiple linear regression analyses were conducted to examine the associations of psychological symptoms and sleep quality parameters with BPV while controlling for age and mean arterial pressure.

**Human Subjects Protection**

This cross-sectional, descriptive, correlational design study, using a survey approach and non-invasive procedure for data collection, was conducted with efforts to protect the human rights of all subjects.

### *IRB Approval and Enrollment of Subjects*

The IRB approval was obtained by the Human Subjects Committee at the UVA Health System (IRB-HSR 22260). After obtaining IRB approval including the approval of consent form, enrollment of subjects was started. The materials for advertisement included a name of the enrolling facility, the purpose of the research, major inclusion/exclusion criteria, a brief list of procedures required, time commitment for participation, contact information, name of PI, and IRB-HSR number. Eligible research participants were provided a consent form according to institutional guidelines. (1) The researcher explained the research aims and procedure to potential participants; (2) The prospective participants was informed that they can withdraw from the study anytime they want to do, and that confidentiality of information is be maintained throughout the study; (3) With voluntary intention to participate in the study, participants signed the informed consent; (4) A copy of the signed informed consent was provided to participants; and (5) the signed informed consent was kept in a locked drawer in a locked room in the School of Nursing which only the PI had access to.

### *Potential Risk and Protection against Risk*

The procedures required for this study presented minimal risk to subjects. The anticipated discomfort and inconvenience were those associated with refraining from consuming coffee, smoking, eating, and vigorous exercise for at least 3 hours and drinking alcohol for 10 hours before data collection; questionnaire completion; sleep and cardiovascular marker measures; and the time required for subjects to participate. All measures included in this study were non-invasive; however, participants might have felt uncomfortable when these measurements were conducted (e.g., wearing actigraphy for 7 days and ambulatory BP monitoring for 24 hours). All study visits took place in a private space of research lab at UVA School of Nursing. The physiological measures were directly entered and saved as electronic files. The electronic files included only the subject's identification number and were saved in a computer to which only the PI had access.

## References

Al-Rawashdeh, S. Y., Lennie, T. A., & Chung, M. L. (2016). Psychometrics of the Zarit Burden Interview in caregivers of patients with heart failure. *The Journal of Cardiovascular Nursing*, *31*(6), E21–E28. https://doi.org/10.1097/JCN.0000000000000348

Cameron, I. M., Crawford, J. R., Lawton, K., & Reid, I. C. (2008). Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *British Journal of General Practice*, *58*(546), 32–36. https://doi.org/10.3399/bjgp08X263794

Gelaye, B., Williams, M. A., Lemma, S., Deyessa, N., Bahretibeb, Y., Shibre, T., Wondimagegn, D., Lemenhe, A., Fann, J. R., Vander Stoep, A., & Andrew Zhou, X. H. (2013). Validity of the patient health questionnaire-9 for depression screening and diagnosis in East Africa. *Psychiatry Research*, *210*(2), 653–661. https://doi.org/10.1016/j.psychres.2013.07.015

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, *16*(9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I., & Struijker-Boudier, H. (2006). Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *European Heart Journal*, *27*(21), 2588–2605. https://doi.org/10.1093/eurheartj/ehl254

Leung, A. A., Nerenberg, K., Daskalopoulou, S. S., McBrien, K., Zarnke, K. B., Dasgupta, K., Cloutier, L., Gelfer, M., Lamarre-Cliche, M., Milot, A., Bolli, P., Tremblay, G., McLean, D., Tobe, S. W., Ruzicka, M., Burns, K. D., Vallee, M., Prasad, G. V. R., Lebel, M., … Rabi, D. M. (2016). Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. *The Canadian Journal of Cardiology*, *32*(5), 569–588. https://doi.org/10.1016/j.cjca.2016.02.066

Löwe, B., Decker, O., Müller, S., Brähler, E., Schellberg, D., Herzog, W., & Herzberg, P. Y. (2008).

Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Medical Care*, *46*(3), 266–274. https://doi.org/10.1097/MLR.0b013e318160d093

Mantua, J., Gravel, N., & Spencer, R. M. C. (2016). Reliability of sleep measures from four personal health monitoring devices compared to research-based actigraphy and polysomnography. *Sensors (Basel, Switzerland)*, *16*(5). https://doi.org/10.3390/s16050646

Marino, M., Li, Y., Rueschman, M. N., Winkelman, J. W., Ellenbogen, J. M., Solet, J. M., Dulin, H., Berkman, L. F., & Buxton, O. M. (2013). Measuring sleep: Accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep*, *36*(11), 1747–1755. https://doi.org/10.5665/sleep.3142

Mossman, S. A., Luft, M. J., Schroeder, H. K., Varney, S. T., Fleck, D. E., Barzman, D. H., Gilman, R., DelBello, M. P., & Strawn, J. R. (2017). The Generalized Anxiety Disorder 7-item scale in adolescents with generalized anxiety disorder: Signal detection and validation. *Annals of Clinical Psychiatry : Official Journal of the American Academy of Clinical Psychiatrists*, *29*(4).

Muntner, P., Shimbo, D., Carey, R. M., Charleston, J. B., Gaillard, T., Misra, S., Myers, M. G., Ogedegbe, G., Schwartz, J. E., Townsend, R. R., Urbina, E. M., Viera, A. J., White, W. B., & Wright, J. T. (2019). Measurement of blood pressure in humans: A scientific statement from the American Heart Association. *Hypertension*, *73*(5), E35–E66. https://doi.org/10.1161/HYP.0000000000000087

O'Brien, E., Parati, G., Stergiou, G., Asmar, R., Beilin, L., Bilo, G., Clement, D., de la Sierra, A., de Leeuw, P., Dolan, E., Fagard, R., Graves, J., Head, G. A., Imai, Y., Kario, K., Lurbe, E., Mallion, J.-M., Mancia, G., Mengden, T., … Zhang, Y. (2014). European Society of Hypertension position paper on ambulatory blood pressure monitoring. *Journal of Hypertension*, *32*(7), 1359–1366. https://doi.org/10.1097/HJH.0b013e328363e964

Östergren, J., & Isaksson, H. (1993). Ambulatory blood pressure monitoring. *Vascular Medicine Review*, *vmr-4*(2), 95–109. https://doi.org/10.1177/1358863X9300400203

RStudio Team. (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL

http://www.rstudio.com/.

Ruiz, M. A., Zamorano, E., García-Campayo, J., Pardo, A., Freire, O., & Rejas, J. (2011). Validity of the GAD-7 scale as an outcome measure of disability in patients with generalized anxiety disorders in primary care. *Journal of Affective Disorders*, *128*(3), 277–286. https://doi.org/10.1016/j.jad.2010.07.010

Schächinger, H., Langewitz, W., Schmieder, R. E., & Rüddel, H. (1989). Comparison of parameters for assessing blood pressure and heart rate variability from non-invasive twenty-four-hour blood pressure monitoring. *Journal of Hypertension. Supplement : Official Journal of the International Society of Hypertension*, *7*(3), S81-4.

Schreiner, A. S., Morimoto, T., Arai, Y., & Zarit, S. (2006). Assessing family caregiver's mental health using a statistically derived cut-off score for the Zarit Burden Interview. *Aging & Mental Health*, *10*(2), 107–111. https://doi.org/10.1080/13607860500312142

Seng, B. K., Luo, N., Ng, W. Y., Lim, J., Chionh, H. L., Goh, J., & Yap, P. (2010). Validity and reliability of the Zarit Burden Interview in assessing caregiving burden. *Annals of the Academy of Medicine, Singapore*, *39*(10), 758–763.

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, *166*(10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

Yong, M., Diener, H.-C., Kaste, M., & Mau, J. (2005). Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. *Stroke*, *36*(12), 2619–2625. https://doi.org/10.1161/01.STR.0000189998.74892.24

Zarit, S. H., Reever, K. E., & Bach-Peterson, J. (1980). Relatives of the impaired elderly: Correlates of feelings of burden. *The Gerontologist*, *20*(6), 649–655.

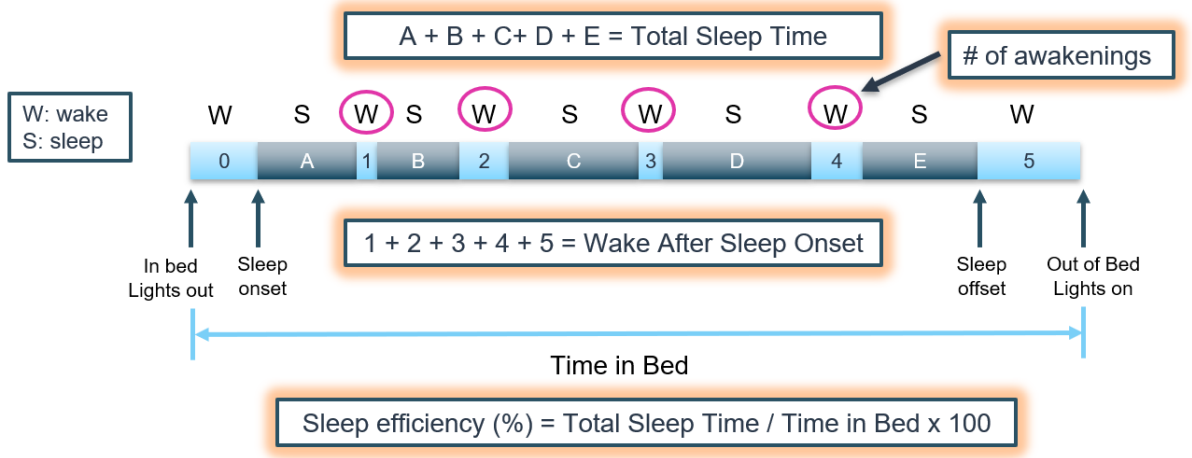
**Table 1**

*Factors, Concepts, Variables, and Measures*

| **Factors** | **Concepts** | **Variables** | **Measures /Measurement Device** | **Time to complete** |
|---|---|---|---|---|
| Individual Characteristics | Age | Age | Self-reported | 30 min |
| | Sex | Sex | Self-reported | |
| | Race/Ethnicity | Race/Ethnicity | Self-reported | |
| | Smoking | Smoking status | Self-reported | |
| | Perceived general health | General health status | Self-reported | |
| | Health conditions | Diagnosis of sleep disorder, diabetes | Self-reported | |
| | Medications | Use of antihypertensive, cholesterol medications | Self-reported | |
| | Body mass index | Weight | Withings electronic scale | |
| | | Height | Accu-Hite wall mounted stadiometer | |
| | Blood pressure | Blood pressure | Omron 3 Series Upper Arm Blood pressure monitor | |
| Caregiving Characteristics | Relationships | Relationships | Self-reported | |
| | Care recipient's health conditions | Care recipient's health conditions | Self-reported | |
| | Caregiving hours | Caregiving hours | Self-reported | |
| | Caregiving period | Caregiving period | Self-reported | |
| Psychological factors | Psychological symptoms | Caregiving stress | Zarit Burden Interview-22 | |
| | | Depression | Patient Health Questionnaire (PHQ)-9 | |
| | | Anxiety | Generalized Anxiety Disorder (GAD)-7 | |
| Behavioral factors | Objective sleep quality | Sleep efficiency | GT9X Link (ActiGraph, Corp., Pensacola, FL) | 7 days |
| | | Wake After Sleep Onset (WASO) | | |
| | | Number of awakenings | | |
| Subclinical CVD marker | Blood pressure variability (BPV) | Short-term BPV: 60-minute interval, 24 hours | SpaceLabs, OnTrak 90227 (SpaceLabs Healthcare, Washington, USA) | 1 day |

**Figure 1**

*Sleep Parameters*



# Chapter 3: Manuscript One

## Cardiovascular Disease Incidence and Risk in Family Caregivers of Adults with Chronic Conditions: A Systematic Review

**Published in the *Journal of Cardiovascular Nursing***

### Citation

Ahn, S., Esquivel, J. H., Davis, E. M., Logan, J. G., & Chung, M. L. (2022). Cardiovascular disease incidence and risk in family caregivers of adults with chronic conditions: A systematic review. *Journal of Cardiovascular Nursing.* 37(3), E47-E60. https://doi: 10.1097/JCN.0000000000000816

**Abstract**

**Background:** Family caregivers experience psychological distress or physical strain that may lead to an increased risk of cardiovascular disease (CVD) morbidity and mortality. Objective: This systematic review aimed to describe the current evidence and gaps in the literature on measures used to assess CVD outcomes in family caregivers, the association of caregiving with CVD incidence/risk outcomes, and associated factors in family caregivers of patients with chronic disease.

**Methods:** Medline, PubMed, CINAHL, Web of Science, and Google Scholar were searched for English-language, peer-reviewed studies published from 2008 to 2020 that examined CVD incidence and risk among family caregivers of adults with chronic conditions.

**Results:** Forty-one studies were included in this review. The measures used to assess CVD risk were categorized into biochemical, subclinical markers, components of metabolic syndrome, and global risk scores. Compared with non-caregivers, caregivers were more likely to have higher CVD incidence rates and objectively measured risk. Cardiovascular disease risks were also increased by their caregiving experience, including hours/duration of caregiving, caregivers' poor sleep status, psychological symptoms, poor engagement in physical/leisure activities, and care recipient's disease severity.

**Conclusions:** Although there were limited longitudinal studies in caregivers of patients with diverse health conditions, we found evidence that caregivers are at high risk of CVD. Further research for various caregiver groups using robust methods of measuring CVD risk is needed. Caregiver factors should be considered in developing interventions aimed at reducing CVD risk for caregivers.

**Keywords:** caregiver burden, cardiovascular diseases, risk factors, biomarkers, systematic review

## Introduction

Family caregivers are a critical link in the U.S. healthcare system. An estimated 53 million adults provide physical, psychological, practical, and social support to their loved ones during an acute or chronic medical illness.[1] Caregivers' contributions had an estimated economic value of $470 billion in 2017.[2] As society ages, and in turn, as the number of people who need care for various chronic conditions grows, the demand for family caregiving is projected to rapidly increase.

Caregivers are known to be vulnerable to declines in psychological and physical health due to continuous caregiving demands and distress. Caregivers have exhibited unfavorable physical health outcomes represented by elevated stress hormone levels, immunologic and metabolic dysfunction, and decline in self-reported health.[3–6] Researchers have especially considered caregivers as a vulnerable population, particularly to cardiovascular disease (CVD), since a longitudinal study reported that caregivers who spent 9 hours or higher per week were at 82% higher risk for coronary heart disease than non-caregivers two decades ago.[7] However, most research focused on the psychological burden of caregiving without connecting their caregiving experience to CVD risk manifestation. Understanding caregivers' CVD vulnerability provides the rationale for CVD risk assessment and management in primary care settings for the population.

Although diverse factors play a part in CVD development, the stress response is regarded as a plausible explanation. That is, physiological systems, including the hypothalamic-pituitary-adrenal axis, autonomic nervous system, and immune system, respond to stress by releasing catecholamine and glucocorticoids, enabling oxidative modification within blood vessels.[8,9] These responses, in turn, promote chronic inflammatory processes and lead to subsequent structural and functional changes in the cardiovascular system, such as atherosclerosis progression.[8,9] This mechanism may also potentially explain CVD risk among caregivers, given that they are likely to be exposed to continuous stress derived from the caregiving role. With important advances in understanding the pathogenesis of CVD, various measures have been used to assess CVD risk and conventional risk factors in diverse populations. A variety of biomarkers have been known to help identify individuals with an excess CVD risk. However,

assessment of CVD risk in the caregiver population has not yet been systematically reported. Because incorporating clinical testing along with traditional risk factor assessment is encouraged for risk assessment for persons at high risk for CVD,[10] addressing current utilization of CVD risk measures for caregivers in research is needed to identify evidence gaps.

Established risk factors for CVD development include physical inactivity, smoking, a high saturated fat/sodium diet, and obesity, to name a few.[11,12] Factors specific to the caregiving context may also contribute to increased CVD risk. Caregivers commonly report not being able to engage in healthy behaviors or having little to no time for self-care due to their caregiving responsibility and psychological distress (e.g., depressive symptoms) related to caregiving.[13,14] These altered behaviors directly or indirectly may have deleterious effects on cardiovascular health, along with psychological stress. However, little is known about what specific factors related to the caregiving context are associated with CVD risk in the last decade. Thus, the specific aims of this systematic review were: (1) to describe measures that have been used to assess CVD risk; (2) to describe the prevalence of CVD incidence and risk; and (3) to identify unique caregiving factors associated with CVD incidence/risk in caregivers of patients with chronic diseases.

## Methods

### Search Strategy

This review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We searched Medline, PubMed, CINAHL, and the Web of Science databases, as well as Google Scholar, for the literature that focused on CVD risk in family caregivers of adults with chronic diseases using these relevant subject heading terms and keywords: (“family caregiver” OR “informal caregiver”) AND (“cardiovascular risk” OR “cardiovascular disease”).

### Inclusion/Exclusion Criteria

Eligibility criteria for included studies were as follows: (1) sampled family caregivers of adults with chronic conditions; (2) examined CVD incidence or risk as an outcome variable; (3) examined factors associated with CVD incidence and risk; (4) reported on primarily collected data; (5) published

from January 2008 to April 2020 in peer-reviewed journals; and (6) written in English. CVD incidence was defined as having a diagnosis of myocardial infarction, angina, heart failure, and stroke. Our definition of CVD risk included a broad range of cardiovascular conditions and comorbidities associated with CVD (e.g., hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome) and global risk of CVD. We also included studies that examined biomarkers indicating subclinical conditions as an outcome. We excluded studies that: (1) had paid or professional caregivers; (2) assessed CVD risk only using self-reported data (e.g., self-reported hypertensive status); and (3) were qualitative or meta-analysis studies, abstracts, letters to the editor, and review studies.

**Study Selection**

Two reviewers (graduate-level students), including the first author (SA) independently conducted selecting eligible studies. We resolved discrepancies through discussion until reaching an agreement. The literature search strategy yielded 1025 publications after removing duplicates (Figure 1).[15] We excluded 980 studies after first reviewing titles and abstracts, resulting in 45 studies. After full-text reading of the remaining studies, we excluded 9 studies for the following reasons: not caregiving context, objective measures not used, and not original research. Later, we retrieved 5 studies that met the inclusion criteria from the reference lists of the initially reviewed studies. Thus, we selected a total of 41 studies meeting the inclusion and exclusion criteria for this review.

**Data Extraction and Synthesis**

Data were extracted from each study and organized using the following standardized categories: study design, sample size, caregiver characteristics (i.e., mean age, gender, race/ethnicity, relationship to care-recipient, caregiving duration/hours), CVD incidence or risk by measures used, and associated factors. The extracted data were formatted consistently across the studies to identify data patterns and compare findings. The results were synthesized for each study aim. This process was conducted in an iterative manner by the first author (SA) and reviewed by two co-authors (JL and MC).

**Quality Assessment**

The studies' quality was appraised by the two reviewers using a standardized study quality

assessment tool for observational cohort and cross-sectional studies from the National Heart, Lung, and Blood Institute.[16] Disagreements were resolved through discussion for a consensus. Each criterion of the tool composed of 14 questions was rated as either yes, no, or other (i.e., cannot determine, not applicable, or not reported). The tool is intended to help judge each bias area, including selection bias, information bias, measurement bias, and confounding for a study, rather than an overall quality score.[16] The assessment results are as follows: 30 studies satisfied 60% or above of the criteria, and the areas of confounding, mostly related to limitations of a cross-sectional design and selection bias, were the criteria that the least number of the reviewed studies met. The assessment results of all the criteria for each study are presented in the Supplemental Content.

## Results

### Overview of Study Characteristics

Of the 41 reviewed studies, 27 (66%) used a cross-sectional design, and 14 (34%) used a longitudinal study design. The majority of the studies were conducted in the US (n = 30, 73%), followed by Europe (Sweden, UK, and Italy)[17–20] and Japan.[21–24] Of the 30 US studies, 23 studies (76%) were from the Alzheimer's Caregiver Study research team that investigated the effects of dementia caregiving on health in San Diego, California.[25,26,35–44,27,45–47,28–34] Despite a high possibility of duplicated samples for each study, we included all the studies in this review as long as one examined a distinct association from another using different measures in order to capture a broad picture of current evidence.

Twenty-seven studies (66%) focused on the caregivers of patients with dementia, 5 studies (12%) on patients with cancer,[19,20,48–50] one study on caregivers of patients who underwent stem cell transplantation,[51] and 8 studies with unspecified types of conditions.[17,18,21,22,24,52–54] The sample sizes ranged from 40 to 283,970 and the mean age of caregivers ranged from 46 to 74 years. The majority of caregivers were female (range 52-100%), spouses or partners (range 41-100%), followed by adult children (range 9-91%), and white race (range 63-96%). The mean duration of caregiving ranged from 1.4 to 6.7 years and the mean hours of daily caregiving ranged from 7.4 to 11.6 hours.

### CVD Outcome Measures

CVD incidence was an outcome variable in 6 studies,[17,18,24,48,49,52] and CVD risk in 35 studies. We categorized measures of CVD risk into 4 types: biochemical markers (n = 12),[25,26,47,55,27–31,44–46] subclinical markers (n = 7),[20,23,32–36] hypertension and metabolic syndrome (n = 13),[19,21,53,56,57,22,37–41,50,51] and global risk scores (n = 4).[42,43,51,54]

*Biochemical markers* included measures of inflammation (c-reactive protein [CRP], tumor necrosis factor-α, and Interleukin 6, 8),[28–30,46,55] coagulability (D-dimer, von Willebrand factor, and plasminogen activator inhibitor-1),[26,29,47] endothelial function (cell adhesion molecule P-selectin, soluble intercellular adhesion molecule-1),[25,44,46] and sympathetic nervous system function (catecholamine),[25,27,31,45] that are all known as systemic responses and CVD precursors.

*Subclinical markers* included flow-mediated dilation,[32,33] carotid plaque,[34] and carotid artery intima-media thickness indicating endothelial function,[35] based on arterial images captured from an ultrasound system with a transducer. Heart rate variability representing autonomic nervous system regulation was also assessed by analyzing R to R intervals with an electrocardiogram (ECG).[20,23,36]

*Hypertension and metabolic syndrome* were most commonly used to examine CVD risk in caregivers. Prevalence of hypertension[21,53] or blood pressure was reported.[19,22,37,38] Components of metabolic syndrome that were assessed in the studies included levels of glucose, insulin, total/high-density lipoprotein cholesterol, triglyceride, high-sensitivity CRP (hs-CRP), BMI, waist circumference, abdominal circumference, and blood pressure.[39–41,50,51,56,57]

*CVD global risk score systems* included the Framingham Stroke/CHD Risk Score, Reynolds Risk Score, and Allostatic Load Index.[42,43,51,54] The Framingham Risk Score to predict the 10-year-risk of stroke and CHD is calculated using age, sex, smoking status, systolic blood pressure, diabetes (for stroke and CHD), use of antihypertensives, history of cardiovascular disease, presence of left ventricular hypertrophy on ECG, atrial fibrillation (for stroke), and total/high density lipoprotein cholesterol (for CHD).[58,59] The Reynolds Risk Score uses hs-CRP, in addition to the profile of CHD risk score, in consideration of inflammation as a component of metabolic syndrome.[60] The Allostatic Load Index is quantified using 10 measures (i.e., systolic/diastolic blood pressure, waist-hip ratio, total/high density

lipoprotein cholesterol, plasma epinephrine/norepinephrine, dehydroepiandrosterone sulfate, glycosylated hemoglobin, and urinary cortisol).[61]

**CVD Incidence in Caregivers**

The findings of CVD incidence are presented in Table 1. The mean follow-up time across the studies was 11.3 years (range 4.6-20 years). Of the 6 studies that examined the CVD incidence, 4 studies compared caregivers with non-caregivers.[18,24,48,52] Caregiving status (caregivers vs. non-caregivers) predicted up to 2 times higher CVD incidence in 3 studies.[24,48,52] Exposure to spousal caregiving more than 14 hours per week predicted 1.4 times higher CVD incidence (i.e., myocardial infarction, CHD, angina, heart failure, and stroke) compared to non-caregivers in a longitudinal study with 8-year follow up.[52] This effect was more pronounced in caregivers who provided care for more than 2 years, having 2 times greater incidence than non-caregivers.[52] In another study that tracked the incidence of CHD and stroke, spousal caregivers of patients with cancer showed a 1.3 times greater risk of CHD and stroke onset than non-caregivers over 20 years of follow-up.[48] The caregiving effects were more significant in caregiver groups of certain types of cancer having high mortality rates, such as pancreatic and lung cancers, than in those of other types of cancer.[48] There was only one study where the CHD incidence (i.e., myocardial infarction and angina) in caregivers was not significantly higher than in non-caregivers; yet, a subgroup of caregivers with poor self-rated mental and physical health yielded 2 times greater risk of CHD onset than non-caregivers.[18]

**CVD Risk in Caregivers**

The findings of CVD risk are presented in Table 2. CVD risk was assessed in 8 longitudinal and 27 cross-sectional studies. We organized the findings by the CVD risk measures.

***Biochemical Markers***

Caregivers had higher inflammatory biomarker levels, including CRP and tumor necrosis factor-α, than non-caregivers.[46,55] Further, elevated CRP levels were associated with caregiving duration. The CRP levels of caregivers who had provided care for 15 years or longer were nearly 2 times greater than in non-caregivers, as well as in those at the beginning of their caregiving role.[46] The CRP levels decreased

when their caregiver role ended due to care-recipient death.[46]

***Subclinical Markers***

Significant differences in subclinical markers between caregivers and non-caregivers were found.[20,23,32,34,36] Caregivers showed a 2.2 times greater risk of having carotid plaque than non-caregivers.[34] Caregivers who provided long-term care (≥ 4 years) and to patients with greater dementia severity had significantly lower levels of endothelial function than non-caregivers.[32] In addition, caregivers exhibited a blunted vagal reflex function and decreased sympatho-vagal balance through lower heart rate variability in comparison to non-caregivers.[20,23,36]

***Hypertension and Metabolic Syndrome***

Compared to non-caregivers, caregivers had a 1.4 times higher rate of incident hypertension and the hypertension risk among long-term caregivers (≥ 2 years) was 2.3 times higher in a longitudinal study.[53] Caregivers also had a higher prevalence of hypertension than non-caregivers in cross-sectional studies,[19,21] one of which found a significant association only among females.[21] Caregiving status was also associated with the prevalence of metabolic syndrome components.[40,41,51,56,57] Very low-density lipoprotein particle concentration, an important indicator of cardiometabolic risk, increased over time in caregivers while remaining stable in non-caregivers.[51] Moreover, caregivers had a greater number of components of metabolic syndrome over time than non-caregivers, which decreased to the level of non-caregivers upon caregiving completion.[40]

***Global Risk Scores***

Significant differences in global risk scores between caregivers and non-caregivers were found. Caregivers showed significantly higher Framingham CHD risk score (8.0 ± 2.9 vs. 6.3 ± 3.0) and the Allostatic Load Index (1.9 ± 0.2 vs. 1.4 ± 0.1) compared to non-caregivers, controlling for confounders including demographics, socioeconomic status, health behavior, and psychological distress.[42,43]

**Factors Associated with CVD Incidence and Risk**

Factors associated with CVD incidence and risk among caregivers were also examined. We categorized the factors into caregiver factors and care-recipient factors. The caregiver factors include

caregiving factors, sleep status, psychological factors, and protective factors.

### *Caregiver Factors*

***Caregiving factors.*** Longer hours and duration of caregiving were associated with worse outcomes. Caregivers who spent 20-69 hours per week providing care had nearly a 1.8 times higher incidence rate of myocardial infarction and angina than non-caregivers.[24] Caregiving for more than 20 hours per week also predicted a 2.6 times higher incidence of CHD and stroke, compared to caregiving for less than 8 hours in another study.[17] The CHD incident rate was found markedly higher among long-term caregivers (≥ 3 years) who provided care for more than 9 hours per week, having a 6.2 times higher incidence rate than those providing care for fewer hours.[17] Furthermore, caregivers who provided care for a longer period of time exhibited higher levels of CRP and catecholamines, as well as more impaired endothelial function and sympatho-vagal balance.[31–33,36,46]

***Sleep status.*** The sleep status of caregivers was also associated with CVD risk.[22,26,29] Higher levels of sleep disruption predicted elevated D-dimer levels that indicate increased coagulability.[26] Poorer sleep quality and shorter objectively measured sleep duration predicted higher inflammatory markers in caregivers.[29] Sleep duration was also inversely associated with mean blood pressure.[22]

***Psychological factors.*** Caregiving stress was associated with CVD risk. Caregivers who had initially reported higher stress levels assessed using the Pearlin Role Overload scale were more likely to develop CVD than their counterparts, who had lower stress levels in an 8-year follow-up study.[62] Higher caregiving stress was also associated with a higher CVD risk represented by the Framingham Stroke Risk score, catecholamine, inflammatory and endothelial markers.[28,33,45,54] Perceived general stress levels among caregivers, measured by a visual analog scale and the Daily Inventory of Stressful Events, were associated with blunted heart rate variability and higher levels of inflammatory markers, respectively.[23,55] Depressive symptoms assessed by the Brief Symptom Inventory were associated with heightened platelet and norepinephrine reactivity in response to an acute stress test.[25,44] Depressive symptoms measured by the Center for Epidemiological Studies-Depression (CES-D) scale also predicted a higher Framingham Risk Score.[54] There was no independent association of depressive symptoms assessed by CES-D with

inflammatory markers in one study; yet, the symptoms were related to higher levels of interleukin-8 when caregivers' satisfaction with leisure activities were taken into account.[30]

***Protective factors.*** Investigators examined factors that could buffer the adverse effects of caregiving on CVD risk. Those protective factors include self-efficacy, personal mastery, and engagement in and satisfaction with leisure/physical activities.[27,28,30,31,33,37,38,41,45] Self-efficacy for coping was found to alleviate the magnitude of caregiving stress effects on CVD risk as measured by levels of interleukin-6.[28] Personal mastery, which was defined as the belief that one has control over life's obstacles, was negatively associated with norepinephrine reactivity in a study.[45] Greater engagement in and satisfaction with leisure activities were associated with lower blood pressure,[38] lower levels of inflammatory markers, and better endothelial function.[30,33] Low perceived activity restriction had a significant interaction between greater engagement in pleasant activities and lower mean arterial blood pressure,[37] whereas higher restriction had an interaction between longer caregiving duration and higher catecholamine levels.[31] Significant moderating effects of leisure satisfaction and physical activity levels on the relationships between caregiving status/hours and CVD risk were also found.[27,41] That is, caregiving hours were positively associated with catecholamine levels at the lower leisure satisfaction but were not found significant with higher levels.[27]

### *Care-Recipient Factors*

The health status of care-recipients with dementia/Alzheimer's disease was associated with their caregivers' CVD risk. Higher dementia severity was associated with impaired endothelial function and higher inflammatory marker levels in caregivers.[26,32] Problematic behaviors of care-recipients and adverse reactions of caregivers to the behaviors were associated with hypercoagulability.[47]

## Discussion

We reviewed 41 articles that provided empirical data concerning CVD incidence/risk and associated factors in the caregiving context. A compelling finding is that, compared to non-caregivers, caregivers of patients with chronic conditions were at a higher CVD incidence risk and more likely to have CVD risk factors. These results suggest caregivers' vulnerability to detrimental cardiovascular

health. The increased CVD risk in otherwise healthy and asymptomatic caregivers underscores the importance of preventing CVD incidence in this population. Although the causality between caregiving and CVD incidence/risk was not proven, a considerable number of studies connecting caregiving to objectively measured CVD risk suggest that caregiving status may be a CVD risk factor.

Various measures have assessed caregiver CVD risk. Among the measures, hypertension itself or components of metabolic syndrome (high blood pressure, high blood sugar, and high cholesterol) were most commonly assessed. Considering that these components are also part of the criteria in the global risk score systems, these conventional risk factors account mostly for CVD risk assessment measures that have been used in caregivers. Biomarkers, particularly representing the stress response process, have increasingly been utilized. In addition, the study findings are in line with emerging evidence on physiological consequences of the response process in the cardiovascular system as a potential mechanism of CVD development.

However, the use of biomarkers in CVD risk assessment is still limited in caregiver studies. Relative to biochemical markers (i.e., inflammation, coagulability, and catecholamine) and metabolic function measures, subclinical markers that measure structural damage to arterial walls and functional changes are not yet widely used. With the reliability of diverse biochemical profiles to predict adverse health outcomes, it should also be noted that these markers are associated with the pathogenesis of numerous diseases. For example, tumor necrosis factor-α is associated with diverse array of inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease.[62,63] Due to their lack of specificity in predicting CVD, these biochemical markers could provide partial data for predicting CVD. According to recent guidelines on the management of blood cholesterol, carotid intima-media thickness is considered one of the "risk-enhancing" factors that alter the extent of risk in subgroups beyond the traditional risk factors, along with metabolic syndrome, lipid abnormalities, and CRP over 2 mg/L.[64] As accumulating evidence points to the prognostic significance of subclinical markers,[65–67] the novel measures of vascular imagining and hemodynamics need more study. Using these types of biomarkers will produce evidence on the potential mechanism and consequence of caregiving on cardiovascular health and on the utility of

the markers as a tool of caregiver CVD risk assessment.

When we examined factors in the caregiving context related to caregivers' CVD risk, caregiver factors (i.e., caregiving hours/duration, sleep status, and psychological symptoms), as well as care-recipient factors (i.e., disease severity and problem behaviors) were associated with CVD risk. Caregiving hours spent per week and caregiving duration were significantly associated with CVD risk. As investigators used different cut-points to distinguish short or long-term of caregiving and various follow-up periods in longitudinal studies, it is not possible to determine the critical time point that caregivers develop CVD and have heightened risks. According to the report of Caregiving in the US 2020, the average caregiving duration is 4.5 years, and the proportion of caregivers who have provided care for 5 years or longer has increased.[1] The critical point where caregivers are likely to experience significant deterioration of cardiovascular health would enable the development of prevention strategies for caregivers. To better understand the long-term impacts of caregiving on cardiovascular health and prevent adverse consequences, further research including larger sample sizes of caregivers from a longitudinal perspective is needed. On the other hand, caregivers' engagement in leisure activities and psychological buffers (i.e., self-efficacy and mastery) played a protective role in the relationship between caregiving and CVD risk. Education and support programs to enhance self-efficacy and personal mastery, which can counteract caregiving's impact on CVD risk, are needed for caregivers to maintain self-care and prevent stress management. Furthermore, studies that follow caregivers throughout a continuum, i.e., from a new transition as a caregiver to completion of caregiving, are also warranted to understand how caregiving duration and the potentially changing psychosocial and environmental factors jointly affect caregivers' health.

This review highlights the importance of modifiable factors, mostly related to health behavior and self-care, in the prevention of caregiver CVD. The modifiable factors would include engagement in leisure or physical activity, quality of sleep, and stress/depression management. In light of traditional CVD risk factors, the undesirable health behavior accompanied by limited time for self-care may place caregivers at greater CVD risk. Improving self-care to engage in positive health behavior is essential.

Still, there remains a dearth of intervention research targeting caregivers' engagement in positive health behaviors to reduce CVD risk and improve CVD outcomes. Previous intervention studies for caregivers' physical health mostly focused on improving physical activity, and few aimed to enhance self-care behaviors.[68,69] It is notable that these studies rarely used objective physical health measures or examined cardiovascular outcomes.

Although stress and depression were significantly associated with CVD,[70] few researchers have investigated the association of caregivers' psychological distress with cardiovascular risk. In addition, how caregivers managed their psychological hardships has not been taken into consideration. In 2019, the American College of Cardiology and American Heart Association's guidelines on the primary prevention of CVD described assessment for psychological stressors and providing appropriate counseling as important considerations for addressing social determinants of cardiovascular health.[71] Self-care engagement, including stress management, needs to be addressed in order for caregivers to promote lifestyle changes that prevent conventional CVD risk factors. It is suggested that exploration of mediating and moderating factors would enhance the utility of existing findings in identifying subgroups at higher risk, as well as developing effective strategies for CVD prevention.[72] The utility could be greater if those factors are modifiable. Thus, studies examining roles of the modifiable psycho-behavioral factors are needed; such studies will inform interventions for enhancing cardiovascular health and support programs for caregivers.

Regarding the characteristics of samples in the included studies, we found significant gaps in the research of caregivers. There was a predominance of white caregivers, ranging from 63-96%, in the studies conducted in the US and European countries. Caregiving burden, tasks, and perception of their role vary depending on racial and cultural differences. For example, compared to white caregivers, racial and ethnic minority caregivers were more likely to report higher caregiving burden and depression with stronger filial obligation beliefs, as well as less use of formal support.[73,74] Because racial health disparities are a critical public health issue, more focus on CVD prevention is needed in minority caregivers. Disproportionately fewer investigators examined CVD risk for caregivers of patients with chronic conditions other than

dementia. Although a high proportion of studies from a single institution might have made this tendency stand out more, it is also true that studies for caregivers of patients with dementia dominate current literature on caregivers' psychological/physical health. Caregivers of patients with stroke, cancer, and Parkinson's disease, conditions likely to be physically demanding, also face significant challenges and physical/psychological strain. Considering the varied caregiving experience by conditions of care-recipients, studies targeting caregivers who provide care to patients with varying chronic conditions are needed.

This review has several implications. Attention to caregivers' vulnerability to CVD is needed in primary care settings. Assessing for modifiable CVD risk factors using education of self-care activities and support programs is critical to maintaining cardiovascular health. The development and testing of interventions aimed at promoting self-care behaviors and enhancing caregivers' cardiovascular health are needed. Robust methods of measuring CVD risk to discover potential pathways in which caregiving affects adverse cardiovascular outcomes and associated factors, especially in high-risk populations and understudied caregiver groups by chronic conditions and types of care-recipients, need to be more utilized.

**Strengths and Limitations**

This systematic review has strengths. It synthesized the most updated research findings of the CVD risk outcomes in caregivers. It also provided evidence on trends in the uses of objective measures to assess caregiver CVD risk and on associated factors of CVD risk specific to the caregiving context. This review provided direction for future research on CVD risk in family caregivers. Nevertheless, several limitations of this review should also be considered. More than half of the reviewed studies came from a research group with only caregivers of patients with Alzheimer's disease. Thus, this may affect the limited representation of the caregiver population. Because we excluded grey literature, non-indexed journals, or articles in non-English languages, there is a potential bias in literature selection that influences the interpretation of results and compromises the generalizability of the evidence. Further, these data are observations where causality cannot be determined.

## Conclusion

Compared to non-caregivers, caregivers are more likely to have higher CVD incidence and risk. The detrimental effect of caregiving on cardiovascular health may occur not only through the continuous stress related to caregiving but also through altered health behavioral factors. In addition, to support caregivers who provide high-intensity caregiving, healthcare providers can assess and determine factors that modify caregivers' lifestyle behaviors to prevent CVD development. More precise stratification of groups with high risk and developing targeted interventions using the associated factors and intermediate processes may help mitigate the adverse impacts of caregiving on CVD risk.

## References


1. National Alliance for Caregiving and AARP. *Caregiving in the U.S. 2020 - AARP Research Report*.; 2020. https://www.caregiving.org/caregiving-in-the-us-2020/. Accessed June 9, 2020.
2. Reinhard SC, Feinberg LF, Houser A, Choula R, Evans M. *Valuing the Invaluable: 2019 Update - AARP Insight on the Issues*.; 2019. https://www.aarp.org/content/dam/aarp/ppi/2019/11/valuing-the-invaluable-2019-update-charting-a-path-forward.doi.10.26419-2Fppi.00082.001.pdf. Accessed June 9, 2020.
3. Davis LL, Weaver M, Zamrini E, Stevens A, Kang D-H, Parker CR. Biopsychological markers of distress in informal caregivers. *Biol Res Nurs*. 2004;6(2):90-99. doi:10.1177/1099800404267353
4. von Kanel R, Dimsdale JE, Mills PJ, et al. Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. *J Gerontol A Biol Sci Med Sci*. 2006;61(9):963-969.
5. Fredman L, Doros G, Cauley JA, Hillier TA, Hochberg MC. Caregiving, metabolic syndrome indicators, and 1-year decline in walking speed: results of Caregiver-SOF. *J Gerontol A Biol Sci Med Sci*. 2010;65(5):565-572. doi:10.1093/gerona/glq025
6. Berglund E, Lytsy P, Westerling R. Health and wellbeing in informal caregivers and non-caregivers: a comparative cross-sectional study of the Swedish general population. *Health Qual Life Outcomes*. 2015;13(1):109. doi:10.1186/s12955-015-0309-2
7. Lee S, Colditz GA, Berkman LF, Kawachi I. Caregiving and risk of coronary heart disease in U.S. women: a prospective study. *Am J Prev Med*. 2003;24(2):113-119. http://www.ncbi.nlm.nih.gov/pubmed/12568816. Accessed July 3, 2019.
8. Wirtz PH, von Kanel R, von Känel R, von Kanel R. Psychological Stress, Inflammation, and Coronary Heart Disease. *Curr Cardiol Rep*. 2017;19(11):111. doi:10.1007/s11886-017-0919-x
9. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav*. 2003;43(1):2-15. doi:10.1016/S0018-506X(02)00024-7
10. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA Guideline for Assessment of

Cardiovascular Risk in Asymptomatic Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2010;56(25):2182-2199. doi:10.1016/j.jacc.2010.09.002

11. Yusuf PS, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet*. 2004;364(9438):937-952. doi:10.1016/S0140-6736(04)17018-9
12. Bowen KJ, Sullivan VK, Kris-Etherton PM, Petersen KS. Nutrition and Cardiovascular Disease—an Update. *Curr Atheroscler Rep*. 2018;20(2):1-11. doi:10.1007/s11883-018-0704-3
13. Gallant MP, Connell CM. Predictors of decreased self-care among spouse caregivers of older adults with dementing illnesses. *J Aging Health*. 1997;9(3):373-395. doi:10.1177/089826439700900306
14. Acton GJ. Health-promoting self-care in family caregivers. *West J Nurs Res*. 2002;24(1):73-86. doi:10.1177/01939450222045716
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
16. Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI). https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed May 5, 2020.
17. Mortensen J, Dich N, Lange T, et al. Weekly hours of informal caregiving and paid work, and the risk of cardiovascular disease. *Eur J Public Health*. 2018;28(4):743-747. doi:10.1093/eurpub/ckx227
18. Buyck J-F, Ankri J, Dugravot A, et al. Informal caregiving and the risk for coronary heart disease: the Whitehall II study. *J Gerontol A Biol Sci Med Sci*. 2013;68(10):1316-1323. doi:10.1093/gerona/glt025
19. Cora A, Partinico M, Munafo M, Palomba D. Health risk factors in caregivers of terminal cancer patients: a pilot study. *Cancer Nurs*. 2012;35(1):38-47. doi:10.1097/NCC.0b013e31820d0c23

20. Lucini D, Cannone V, Malacarne M, et al. Evidence of autonomic dysregulation in otherwise healthy cancer caregivers: a possible link with health hazard. *Eur J Cancer*. 2008;44(16):2437-2443. doi:10.1016/j.ejca.2008.08.006

21. Torimoto-Sasai Y, Igarashi A, Wada T, Ogata Y, Yamamoto-Mitani N. Female family caregivers face a higher risk of hypertension and lowered estimated glomerular filtration rates: a cross-sectional, comparative study. *BMC Public Health*. 2015;15:177. doi:10.1186/s12889-015-1519-6

22. Tsukasaki K, Makimoto K, Kido T. The impact of sleep on ambulatory blood pressure of female caregivers providing home care in Japan: an observational study. *Int J Nurs Stud*. 2008;45(12):1721-1730. doi:10.1016/j.ijnurstu.2008.04.006

23. Sakurai S, Onishi J, Hirai M. Impaired autonomic nervous system activity during sleep in family caregivers of ambulatory dementia patients in Japan. *Biol Res Nurs*. 2015;17(1):21-28. doi:10.1177/1099800414524050

24. Miyawaki A, Tomio J, Kobayashi Y, Takahashi H, Noguchi H, Tamiya N. Impact of long-hours family caregiving on non-fatal coronary heart disease risk in middle-aged people: Results from a longitudinal nationwide survey in Japan. *Geriatr Gerontol Int*. 2017;17(11):2109-2115. doi:10.1111/ggi.13061

25. Aschbacher K, Mills PJ, Känel R von, et al. Effects of depressive and anxious symptoms on norepinephrine and platelet P-selectin responses to acute psychological stress among elderly caregivers. *Brain Behav Immun*. 2008;22(4):493-502. doi:10.1016/J.BBI.2007.10.002

26. Mills PJ, Ancoli-Israel S, von Kanel R, et al. Effects of gender and dementia severity on Alzheimer's disease caregivers' sleep and biomarkers of coagulation and inflammation. *Brain Behav Immun*. 2009;23(5):605-610. doi:10.1016/j.bbi.2008.09.014

27. Chattillion EA, Mausbach BT, Roepke SK, et al. Leisure activities, caregiving demands and catecholamine levels in dementia caregivers. *Psychol Health*. 2012;27(10):1134-1149. doi:10.1080/08870446.2011.637559

28. Mausbach BT, von Kanel R, Roepke SK, et al. Self-efficacy buffers the relationship between

dementia caregiving stress and circulating concentrations of the proinflammatory cytokine interleukin-6. *Am J Geriatr Psychiatry*. 2011;19(1):64-71. doi:10.1097/JGP.0b013e3181df4498

29. von Kanel R, Ancoli-Israel S, Dimsdale JE, et al. Sleep and biomarkers of atherosclerosis in elderly Alzheimer caregivers and controls. *Gerontology*. 2010;56(1):41-50. doi:10.1159/000264654

30. von Kanel R, Mausbach BT, Mills PJ, et al. Longitudinal Relationship of Low Leisure Satisfaction but not Depressive Symptoms With Systemic Low-Grade Inflammation in Dementia Caregivers. *Journals Gerontol Ser B Psychol Sci Soc Sci*. 2014;69(3):397-407. doi:10.1093/geronb/gbt020

31. Ho JS, Bordon J, Wang V, et al. Reduced activity restriction buffers the relations between chronic stress and sympathetic nervous system activation. *J Gerontol B Psychol Sci Soc Sci*. 2014;69(3):408-416. doi:10.1093/geronb/gbt028

32. Mausbach BT, Roepke SK, Ziegler MG, et al. Association between chronic caregiving stress and impaired endothelial function in the elderly. *J Am Coll Cardiol*. 2010;55(23):2599-2606. doi:10.1016/j.jacc.2009.11.093

33. Mausbach BT, Chattillion E, Roepke SK, et al. A longitudinal analysis of the relations among stress, depressive symptoms, leisure satisfaction, and endothelial function in caregivers. *Heal Psychol*. 2012;31(4):433-440. doi:10.1037/a0027783

34. Roepke SK, Chattillion EA, von Känel R, et al. Carotid plaque in Alzheimer caregivers and the role of sympathoadrenal arousal. *Psychosom Med*. 2011;73(2):206-213. doi:10.1097/PSY.0b013e3182081004

35. Roepke S, Allison M, Von Kanel R, et al. Relationship between chronic stress and carotid intima-media thickness (IMT) in elderly Alzheimer's disease caregivers. *Stress*. 2012;15(2):121-129. doi:10.3109/10253890.2011.596866

36. Wu KK, Bos T, Mausbach BT, et al. Long-term caregiving is associated with impaired cardiovagal baroreflex. *J Psychosom Res*. 2017;103:29-33. doi:10.1016/j.jpsychores.2017.10.001

37. Chattillion EA, Ceglowski J, Roepke SK, et al. Pleasant events, activity restriction, and blood

pressure in dementia caregivers. *Health Psychol*. 2013;32(7):793-801. doi:10.1037/a0029412

38. Mausbach BT, Romero-Moreno R, Bos T, et al. Engagement in Pleasant Leisure Activities and Blood Pressure: A 5-Year Longitudinal Study in Alzheimer Caregivers. *Psychosom Med*. 2017;79(7):735-741. doi:10.1097/PSY.0000000000000497
39. Schwartz J, Allison MA, Ancoli-Israel S, et al. Sleep, type 2 diabetes, dyslipidemia, and hypertension in elderly Alzheimer's caregivers. *Arch Gerontol Geriatr*. 2013;57(1):70-77. doi:10.1016/j.archger.2013.02.008
40. von Kanel R, Mausbach BT, Dimsdale JE, et al. Cardiometabolic effects in caregivers of nursing home placement and death of their spouse with Alzheimer's disease. *J Am Geriatr Soc*. 2011;59(11):2037-2044. doi:10.1111/j.1532-5415.2011.03634.x
41. von Kanel R, Mausbach BT, Dimsdale JE, et al. Regular physical activity moderates cardiometabolic risk in Alzheimer's caregivers. *Med Sci Sports Exerc*. 2011;43(1):181-189. doi:10.1249/MSS.0b013e3181e6d478
42. Roepke S, Mausbach B, Patterson T, et al. Effects of Alzheimer Caregiving on Allostatic Load. *J Health Psychol*. 2011;16(1):58-69. doi:10.1177/1359105310369188
43. von Kanel R, Mausbach BT, Patterson TL, et al. Increased Framingham Coronary Heart Disease Risk Score in dementia caregivers relative to non-caregiving controls. *Gerontology*. 2008;54(3):131-137. doi:10.1159/000113649
44. Aschbacher K, Roepke SK, von Kanel R, et al. Persistent versus transient depressive symptoms in relation to platelet hyperactivation: a longitudinal analysis of dementia caregivers. *J Affect Disord*. 2009;116(1-2):80-87. doi:10.1016/j.jad.2008.11.008
45. Roepke SK, Mausbach BT, Aschbacher K, et al. Personal mastery is associated with reduced sympathetic arousal in stressed Alzheimer caregivers. *Am J Geriatr Psychiatry*. 2008;16(4):310-317. doi:10.1097/JGP.0b013e3181662a80
46. von Kanel R, Mills PJ, Mausbach BT, et al. Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal

study. *Gerontology*. 2012;58(4):354-365. doi:10.1159/000334219

47. von Kanel R, Mausbach BT, Dimsdale JE, et al. Problem behavior of dementia patients predicts low-grade hypercoagulability in spousal caregivers. *J Gerontol A Biol Sci Med Sci*. 2010;65(9):1004-1011. doi:10.1093/gerona/glq073

48. Ji J, Zoller B, Sundquist K, Sundquist J. Increased risks of coronary heart disease and stroke among spousal caregivers of cancer patients. *Circulation*. 2012;125(14):1742-1747. doi:10.1161/CIRCULATIONAHA.111.057018

49. Kim Y, Carver C, Shaffer K, Gansler T, Cannady R. Cancer caregiving predicts physical impairments: roles of earlier caregiving stress and being a spousal caregiver. *Cancer*. 2015;121(2):302-310. doi:10.1002/cncr.29040

50. Steel JL, Cheng H, Pathak R, et al. Psychosocial and Behavioral Pathways of Metabolic Syndrome in Cancer Caregivers. *Psychooncology*. June 2019. doi:10.1002/pon.5147

51. Ross A, Shamburek R, Wehrlen L, et al. Cardiometabolic risk factors and health behaviors in family caregivers. *PLoS One*. 2017;12(5):e0176408-e0176408. doi:10.1371/journal.pone.0176408

52. Capistrant BD, Moon JR, Berkman LF, Glymour MM. Current and long-term spousal caregiving and onset of cardiovascular disease. *J Epidemiol Community Health*. 2012;66(10):951-956. doi:10.1136/jech-2011-200040

53. Capistrant BD, Moon JR, Glymour MM. Spousal caregiving and incident hypertension. *Am J Hypertens*. 2012;25(4):437-443. doi:10.1038/ajh.2011.232

54. Haley WE, Roth DL, Howard G, Safford MM. Caregiving Strain and Estimated Risk for Stroke and Coronary Heart Disease Among Spouse Caregivers Differential Effects by Race and Sex. *Stroke*. 2010;41(2):331-336. doi:10.1161/STROKEAHA.109.568279

55. Gouin J-P, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser J. Chronic stress, daily stressors, and circulating inflammatory markers. *Heal Psychol*. 2012;31(2):264-268. doi:10.1037/a0025536

56. Kring SII, Brummett BH, Barefoot J, et al. Impact of psychological stress on the associations

between apolipoprotein E variants and metabolic traits: findings in an American sample of caregivers and controls. *Psychosom Med*. 2010;72(5):427-433. doi:10.1097/PSY.0b013e3181de30ad

57. Madaleno TR, Moriguti JC, Ferriolli E, De Carlo MMRP, Lima NKC. Mood, lifestyle and cardiovascular risk factors among older caregivers of patients with Alzheimer's disease dementia: a case–control study. *Aging Clin Exp Res*. 2019;31(11):1609-1614. doi:10.1007/s40520-019-01212-8

58. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation*. 1998;97(18):1837-1847. doi:10.1161/01.CIR.97.18.1837

59. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: A risk profile from the framingham study. *Stroke*. 1991;22(3):312-318. doi:10.1161/01.STR.22.3.312

60. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: The Reynolds Risk Score. *J Am Med Assoc*. 2007;297(6):611-619. doi:10.1001/jama.297.6.611

61. Seeman TE. Price of Adaptation—Allostatic Load and Its Health Consequences. *Arch Intern Med*. 1997;157(19):2259. doi:10.1001/archinte.1997.00440400111013

62. Pachot A, Arnaud B, Marrote H, et al. Increased tumor necrosis factor-alpha mRNA expression in whole blood from patients with rheumatoid arthritis: reduction after infliximab treatment does not predict response. *J Rheumatol*. 2007;34(11):2158-2161. http://www.ncbi.nlm.nih.gov/pubmed/17896807. Accessed April 1, 2019.

63. Ruder B, Atreya R, Becker C. Tumour necrosis factor alpha in intestinal homeostasis and gut related diseases. *Int J Mol Sci*. 2019;20(8). doi:10.3390/ijms20081887

64. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of

Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):E1082-E1143. doi:10.1161/CIR.0000000000000625

65. Hillebrand S, Gast KB, de Mutsert R, et al. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose–response meta-regression. *EP Eur*. 2013;15(5):742-749. doi:10.1093/europace/eus341

66. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55(13):1318-1327. doi:10.1016/j.jacc.2009.10.061

67. Wang J, Shi X, Ma C, et al. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. *J Hypertens*. 2017;35(1):10-17. doi:10.1097/HJH.0000000000001159

68. Elliott AF, Burgio LD, Decoster J. Enhancing caregiver health: Findings from the resources for enhancing Alzheimer's Caregiver Health II intervention. *J Am Geriatr Soc*. 2010;58(1):30-37. doi:10.1111/j.1532-5415.2009.02631.x

69. Lambert SD, Duncan LR, Kapellas S, et al. A Descriptive Systematic Review of Physical Activity Interventions for Caregivers: Effects on Caregivers' and Care Recipients' Psychosocial Outcomes, Physical Activity Levels, and Physical Health. *Ann Behav Med*. 2016;50(6):907-919. doi:10.1007/s12160-016-9819-3

70. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. *Am J Hypertens*. 2015;28(11):1295-1302. doi:10.1093/ajh/hpv047

71. Arnett DK, Roger Blumenthal C-CS, Michelle Albert C-CA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;3. doi:10.1161/CIR.0000000000000678

72. BaumA. Behavioral and psychosocial intervention to modify pathophysiology and disease course. In: Smedley BD, Syme LS, eds. Promoting Health: Intervention Strategies from Social and Behavioral Research.Washington,DC:National Academies Press; 2000:450–488.

73. Sander AM, Davis LC, Struchen MA, et al. Relationship of race/ethnicity to caregivers' coping, appraisals, and distress after traumatic brain injury. *NeuroRehabilitation*. 2007;22(1):9-17.

74. Pinquart M, Sörensen S. Ethnic Differences in Stressors, Resources, and Psychological Outcomes of Family Caregiving: A Meta-Analysis. *Gerontologist*. 2005;45(1):90-106. doi:10.1093/geront/45.1.90

Table 1
Incidence of Cardiovascular Disease and Associated Factors in Caregivers

| Authors | Research design | Caregiver characteristics | Care-recipient diagnosis | Type of CVD | Significant findings |
|---|---|---|---|---|---|
| *Buyck et al. (2013)[18] | Longitudinal (a mean of 17 years) | CG (n=862) vs.NC (n=7,063)<br>Age(mean)=51.1; Female (40%); White (95%) | Not specified | Nonfatal myocardial infarction and angina | CG with poor self-rated, mental, or physical health 1.6-2 times ↑ (vs. NC in good health) |
| *Capistrant et al. (2012)[52] | Longitudinal (up to 8 years) | CG (n=317) vs. NC (n=8,155)<br>Age= 63.9; Female (52%); White (88%) | Not specified | Heart attack, CHD, angina, congestive heart failure, and stroke | CG, 1.4 times ↑; long-term CG, 2 times ↑ |
| *Ji et al. (2012)[48] | Longitudinal (up to 20 years) | CG: N=283,970<br>Age (median): male, 66; female 67 | Cancer | CHD and stroke | Cancer diagnosis of spouses, 1.1-1.3 times ↑ (vs. those with no cancer diagnosis) |
| *Kim et al. (2015)[62] | Longitudinal (8 years) | CG: N=1,517<br>Age=55.0; Female (64.9%); White (92.7%) | Cancer | angina, CHD, cardiac arrest, congestive heart failure, heart attack, heart murmur, irregular heartbeat, and pacemaker | Greater stressed CG at baseline, more likely to develop CVD over time (vs. lower stressed CG) |
| *Miyawaki et al. (2017)[24] | Longitudinal (a mean of 4.6 years) | CG (n=2,100) vs. NC (n=23,021)<br>Age=50-59; Female (51.9%) | Not specified | Myocardial infarction and angina | CG spent 20-69 hour per week 1.78 time ↑ (vs. NC) |
| *Mortensen et al. (2018)[17] | Longitudinal (10 years) | CG: N=1,396<br>Age=51.0; Female (54.0%) | Not specified | CHD and stroke | Care>20hr weekly, 2.6 times ↑ (vs. 1-8hr weekly); long-term CG (≥3 years), 6.2 times ↑ (vs. short-term caregivers);<br>Care>8hr and working <40hr weekly, 3 times ↑ (vs. care 1-8hr and working < 40hr) |

Abbreviations: CHD, coronary heart disease; CG, caregivers; CVD, cardiovascular disease; NC, non-caregivers
*Studies met 60% or above of the criteria of quality assessment (9 or more criteria rated "yes")

Table 2
Cardiovascular Disease Risk and Associated Factors in Caregivers by Measures

| Authors | Research design | Caregiver characteristics | Care-recipient diagnosis | Measures of CVD risk | Significant findings |
|---|---|---|---|---|---|
| ***Biochemical markers*** | | | | | |
| Aschbacher et al. (2008)[25] | Cross-sectional | CG (n=39) vs. NC (n=31)<br>Age=68.7; Female (64%); White (93%) | Dementia | Norepinephrine<br>Cell adhesion molecule PSEL (following acute stress test) | Depression and anxiety − norepinephrine recovery (↓, *P*=.008; *P*=.034), PSEL responses reactivity (↑, *P*<.001; *P*=.002), PSEL responses recovery (↓, *P*=.039; *P*=.092) in CG<br>Depressive symptoms mediate role overload and PSEL responses reactivity (*P*=.008) |
| *Aschbacher et al. (2009)[44] | Longitudinal | CG: N=99<br>Age=73.0; Female (68%); White (93%) | Dementia | Cell adhesion molecule PSEL (following acute stress test) | Persistent depressive symptoms − platelet reactivity (↑) |
| *Chattillion et al. (2012)[27] | Cross-sectional | CG: N=107<br>Age=74.0; Female (68%); White (94%) | Dementia | Norepinephrine<br>Epinephrine | Caregiving hours-by-leisure satisfaction − norepinephrine (↑, *P*=.005) and epinephrine (↑, *P*=.003) |
| Gouin et al. (2012)[55] | Cross-sectional | CG (n=53) vs. NC (n=77)<br>Age=64.3; Female (80.0%); White (79%) | Dementia | CRP, IL-6 | CG, CRP levels (↑, *P*=.03).<br>Daily stressors − serum IL-6 (↑, *P*=.04) and CRP (↑, *P*=.04)<br>Daily stressors partially mediate caregiving and CRP (*P*=.02) |
| *Mausbach et al. (2011)[28] | Cross-sectional | CG: N=62<br>Age=74.2; Female (71%) | Dementia | IL-6 | Self-efficacy (↓)-by-stress (↑) − IL-6 (↑) |
| *Mills et al. (2009)[26] | Cross-sectional | CG (n=81) vs. NC (n=41)<br>Age (male, 75.6-77.8; female, 68.5-71.3); Female (71.6%); White (89%) | Dementia | IL-6, D-dimer | Male CG of spouses with worse dementia, D-dimer (↑, *P*=.034) than females.<br>Dementia severity (↑, *P*=.047), awake after sleep onset (↑, *P*=.046) − D-dimer (↑) |
| *Roepke et al. (2008)[45] | Cross-sectional | CG: N=68<br>Age=72.8; Female (66%); White (93%) | Dementia | Norepinephrine | Mastery − norepinephrine reactivity (↓, *P*=.046) |
| *von Kanel | Cross-sectional | CG (n=97) vs. NC (n=48) | Dementia | D-dimer, VWF, IL- | Subjective sleep quality (↓) − levels of fibrin |

| | | | | | |
|---|---|---|---|---|---|
| et al. (2010)[29] | | Age=72.4; Female (71%) | | 6, CRP | D-dimer (↑, *P*=.022), VWF antigen (↑, *P*=.029)<br>CG, stronger correlation between percent sleep and elevated levels of IL-6 and CRP |
| *von Kanel et al. (2010)[47] | Cross-sectional | CG: N=108<br>Age=73.8; Female (70%) | Dementia | D-dimer, VWF, PAI-1 | Number of problem behaviors (↑, *P*=.014) and negative reactions of CG to these behaviors (↑, *P*=.017) − procoagulant index (↑) |
| *von Kanel et al. (2012)[46] | Longitudinal | CG (n=118) vs. NC (n=51)<br>Age=74.4; Female (70%); White (92%) | Dementia | CRP, TNF-α , sICAM-1 | Duration of caregiving − CRP levels (↑, *P*=.040)<br>CG, TNF-α levels (↑, *P*=.048)<br>Death of the spouse − CRP levels (↓, *P*=.003), sICAM-1 (↓, *P*=.008) |
| *Ho et al. (2014)[31] | Cross-sectional | CG: N=84<br>Age=70.7; Female (75%); White (86.9%) | Dementia | Norepinephrine<br>Epinephrine | Years of caregiving, activity restriction – epinephrine (↑)<br>Years of caregiving-by-activity restriction – epinephrine (↑) |
| *von Kanel et al. (2014)[30] | Longitudinal | CG: N=121<br>Age=74.3; Female (69.5%) | Dementia | TNF-α, IL-6, 8, IFG | Leisure activity satisfaction (↑) − TNF-α (↓, *P*=.047), IL-8 (↓, *P*<.001), IFG (↓, *P*=.020).<br>Enjoyment (↓) − TNF-α (↑, *P*=.045), IL-8 (↑, *P* < .001), IFG (↑, *P*=.002); frequency (↓) − IL-8 (↑, *P*=.023). |
| ***Subclinical markers*** | | | | | |
| Lucini et al. (2008)[20] | Cross-sectional | CG (n=58) vs. NC (n=60)<br>Age=45.7; Female (51.7%) | Cancer | Heart rate variability | CG, HF of RR interval (↓), LF/HF ratio (↑), index alpha representing baroreflex (↓) (p < .05) (vs. NC) |
| *Mausbach et al. (2010)[32] | Cross-sectional | CG (n=35) vs. NC (n =23)<br>Age=74.2; Female (69.0%); White (91%) | Dementia | Impaired FMD | Moderate to severe dementia, FMD (↓) (vs. mild dementia, *P*=.028; NC, *P*=.032)<br>Years of caregiving − FMD (↓, *P* < .001) |
| *Mausbach et al. (2012)[33] | Longitudinal | CG: N = 116<br>Age=74.3; Female (68%); White (87%) | Dementia | Impaired FMD | Leisure satisfaction (↑), stress (↓, *P*=.017) − FMD (↑, *P*=.050)<br>Years of caregiving (↑) − FMD (↓, *P*=.027) |
| Roepke et al. (2011)[34] | Cross-sectional | CG (n = 111) vs. NC (n = 51)<br>Age=73.6; Female (69%); White | Dementia | Carotid plaque | CG, 2 times higher presence of plaque (vs. NC) |

| | | | | | |
|---|---|---|---|---|---|
| | | (92%) | | | Recovery of epinephrine (↓) − the presence of plaque (↑, *P*=.04) in CG |
| *Roepke et al. (2012)[35] | Cross-sectional | CG: N = 110<br>Age=73.7; Female (69%); White (93%) | Dementia | Carotid artery IMT | Duration of care − IMT in the internal/bifurcation segments of the carotid artery (↑, *P*=.044) |
| Sakurai et al. (2015)[23] | Cross-sectional | CG (n = 20) vs. NC (n =20)<br>Age=60.0; Female (80%) | Dementia | Heart rate variability (HF, LF/HF ratio) | CG, LF/HF ratio (↑, vs. NC) during sleep: higher levels of sympathetic nervous system activity (*P*=.048)<br>CG, perceived stress – HF (↓): lower levels of parasympathetic nervous system activity |
| *Wu et al. (2017)[36] | Cross-sectional | CG (n = 96) vs. NC (n = 50)<br>Age=72.9-74.4; Female (77.1%) | Dementia | cBRS | Long-term CG (≥ 4 years), impaired cBRS (*P*=.013; vs. NC) |
| ***Hypertension and metabolic syndrome*** | | | | | |
| *Capistrant et al. (2012)[53] | Longitudinal | CG (n = 1,042) vs. NC (n = 4,466)<br>Age=66.5-66.9; Female (51.9%); White (95.6%) | Not specified | Hypertension incidence | CG, 1.4 times ↑; long-term CG, 2.3 times ↑ |
| *Chattillion et al. (2013)[37] | Cross-sectional | CG: N = 66<br>Age=71.2; Female (76%); White (85%) | Dementia | BP | Engagement in pleasant events (↑), activity restriction (↓) − mean BP (↓) (vs. other combinations of engagement and restriction, *P*<.05). |
| *Cora et al. (2012)[19] | Cross-sectional (pilot study) | CG (n=20) vs. NC (n=20)<br>Age=50.1; Female (90%) | Terminal cancer | BP, HR | CG, prehypertensive or hypertensive stage, 25% (vs. NC, 10%)<br>CG, BP (↑) (vs. NC)<br>Caregiving duration (↑) – HR (↑) |
| Kring et al. (2010)[56] | Cross-sectional | CG (n=126) vs. NC (n=122)<br>Age=63.2; Female (75%) | Dementia | Metabolic traits | C/T genotype-by-caregivers stress − metabolic variables<br>T/T genotype − waist circumference (↑), triglycerides (↑), and HDL (↓) in CG |
| *Madaleno et al. (2019)[57] | Cross-sectional (case-control) | CG (n=31) vs. NC (n=31)<br>Age=69.4; Female (100%) | Dementia | Metabolic syndrome components | CG, total cholesterol, 3.6 times higher rate of elevated level (vs. NC) |
| *Mausbach et al. (2017)[38] | Longitudinal | CG: N=126<br>Age=74.2; Females (71%) | Dementia | BP | Engagement in leisure activities (↑) − mean BP (↓, *P*=.040).<br>Placement or death of the patient − mean BP (↓, *P*=.005; *P*=.021) |

| | | | | | |
|---|---|---|---|---|---|
| Ross et al. (2017)[51] | Longitudinal | CG (n=21) vs. NC (n=20)<br>Age=52.2; Female (57%) | Adults undergoing stem cell transplantation | Metabolic syndrome components, Reynold Risk Score | Very low-density lipoprotein particle concentration ↑ over time in CG (vs. NC, *P*=.016).<br>Caregiving − LDL particle size (*P*=.012) |
| *Schwartz et al. (2013)[39] | Cross-sectional | CG: N=126<br>Age=74.2; Female (71%); White (92%) | Dementia | Metabolic syndrome components | No significant relationship with sleep duration, sleep efficiency, or daytime naps |
| *Steel et al. (2019)[50] | Cross-sectional | CG: N=104<br>Age=59.5; Female (77%); White (94%) | Cancer | Metabolic syndrome components | 49% of CG: met metabolic syndrome criteria |
| *Torimoto-Sasai et al. (2015)[21] | Cross-sectional | CG (n=149) vs. NC (n=149)<br>Age=61.4-67.3; Female (70.5%) | Not specified | Hypertension | Prevalence of high BP: CG, 2 times ↑ in females |
| Tsukasaki et al. (2008)[22] | Cross-sectional | CG: N=78<br>Age=62.5; Female (100%) | Not specified | Ambulatory blood pressure | Hours of sleep (↓) − mean systolic BP (↑) |
| *von Kanel et al. (2011)[40] | Longitudinal | CG (n = 119) vs. NC (n = 55)<br>Age=74.4; Female (70%) | Dementia | Metabolic syndrome components | CG, number of components ↑ over time (vs. NC, *P*=.008)<br>Death of the spouse − the number of components (↓)<br>Placement of the spouse-by-depressive symptoms (↓) and placement of the spouse-by-sleeping difficulties (↓) − the number of components (*P*=.01; *P*=.02) |
| *von Kanel et al. (2011)[41] | Cross-sectional | CG (n=115) vs. NC (n=54)<br>Age=73.8; Female (70%) | Dementia | Metabolic syndrome components | CG, standardized cardiometabolic risk score ↑<br>Caregiving-by-levels of physical activity (↓) − cardiometabolic risk score (↑) (*P*=.017). |
| ***Global risk scores*** | | | | | |
| *Haley et al. (2010)[54] | Cross-sectional | Stroke risk, CG: n=716<br>CHD risk, CG: n=607<br>Age=67.9; Female (55%); White (63%) | Not specified | Framingham Stroke Risk Score, Framingham CHD Risk Score | Caregiving strain (↑) − stroke risk score (↑)<br>Stronger association in African American men |
| *Roepke et al. (2011)[42] | Cross-sectional | CG (n=87) vs. NC (n=43)<br>Age=74.3; Female (71%); White (95.4%) | Dementia | Allostatic load index | CG, allostatic load index (↑, 1.9 vs. 1.4, *P* < .05)<br>Mastery-by-caregiving − allostatic load (↑) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | (*P*=.013) |
| von Kanel et al. (2008)[43] | Cross-sectional | CG (n=64) vs. NC (n=41) Age=72.7; Female (72%); White (91%) | Dementia | Framingham CHD Risk Score | CG, CHD risk scores (↑, 7.97±2.90 vs, 6.32±3.03, *P*=.013, *d*=0.57) |

Abbreviations: BP, blood pressure; cBRS, cardiovagal baroreflex sensitivity; CHD, coronary heart disease; CG, caregivers; CRP, C-reactive protein; CVD, cardiovascular disease; FMD, flow-mediated dilation; HDL, high-density lipoprotein; HF, high frequency; HR, heart rate; IFG, Interferon-γ; IL, interleukin; IMP, intima-media thickness; LDL, low-density lipoprotein; LF, low frequency; NC, non-caregiver; PAI, plasminogen activator inhibitor; PSEL, P-selectin; sICAM, soluble intercellular adhesion molecule; TNF, tumor necrosis factor; VWF, von Willebrand factor

*Studies met 60% of the criteria of quality assessment (9 or more criteria rated "yes")

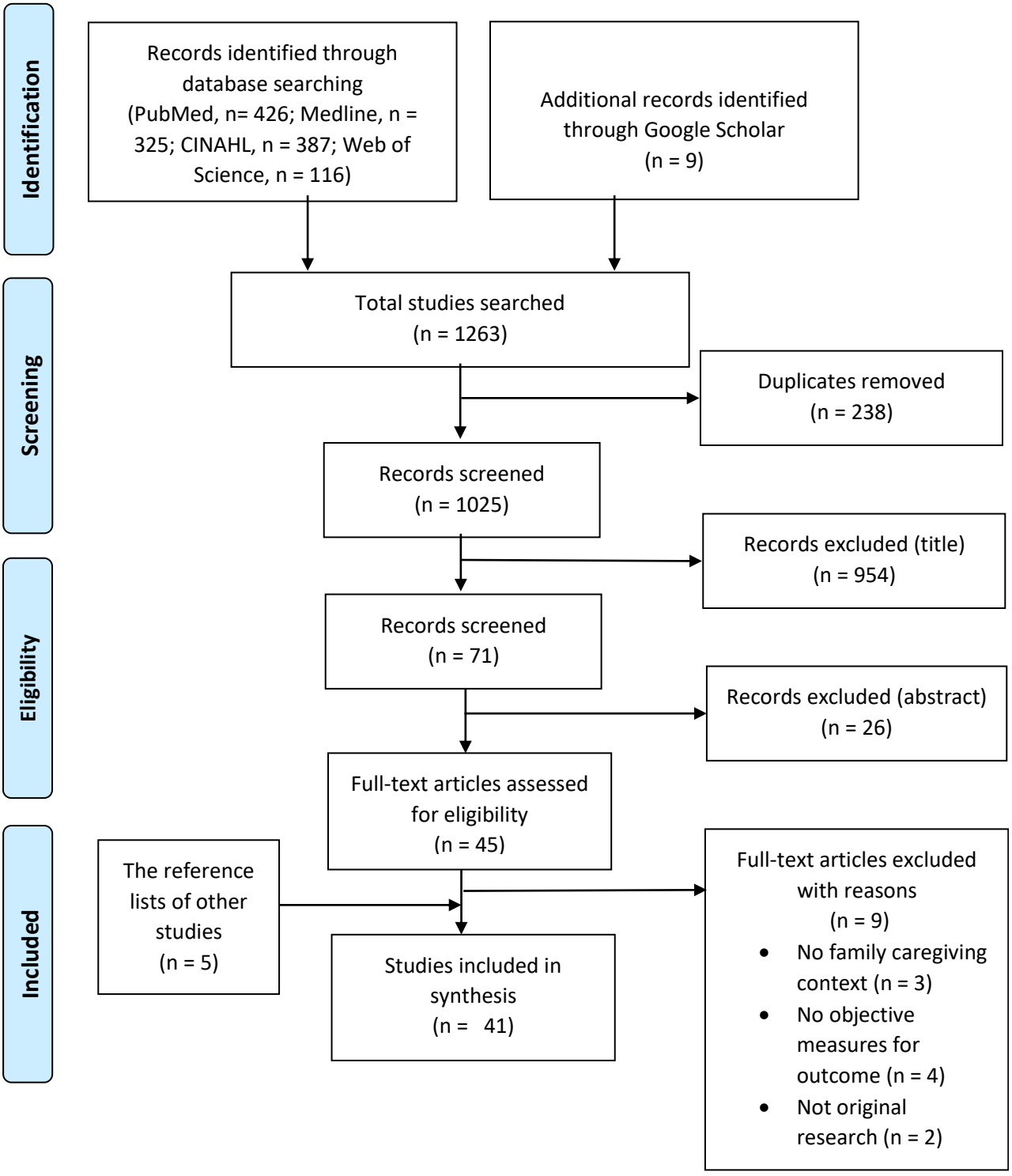



Figure 1. PRISMA flow diagram for study selection.

Supplement 1. Quality Appraisal of Included Studies

| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Buyck et al. (2013) | Capistrant et al. (2012) | Ji et al. (2012) | Kim et al. (2015) | Miyawaki et al. (2016) | Mortensen et al. (2018) | Aschbacher et al. (2008) | Aschbacher et al. (2009) | Chattillion et al. (2012) | Gouin et al. (2012) |
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Was the participation rate of eligible persons at least 50%? | Yes | Yes | Yes | Yes | Yes | Yes | CD | CD | Yes | CD |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | NR |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | No | No |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous | Yes | Yes | NA | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Buyck et al. (2013) | Capistrant et al. (2012) | Ji et al. (2012) | Kim et al. (2015) | Miyawaki et al. (2016) | Mortensen et al. (2018) | Aschbacher et al. (2008) | Aschbacher et al. (2009) | Chattillion et al. (2012) | Gouin et al. (2012) |
| variable)? | | | | | | | | | | |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10. Was the exposure(s) assessed more than once over time? | No | Yes | No | Yes | No | No | No | Yes | No | No |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 13. Was loss to follow-up after baseline 20% or less? | Yes | Yes | Yes | No | Yes | Yes | NA | No | NA | NA |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

Supplement 1. Quality Appraisal of Included Studies (Continued)

| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mausbach et al. (2011) | Mills et al. (2009) | Roepke et al. (2008) | von Kanel et al. (2010) | von Kanel et al. (2010) | von Kanel et al. (2012) | Ho et al. (2014) | von Kanel et al. (2014) | Lucini et al. (2008) | Mausbach et al. (2010) |
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Was the participation rate of eligible persons at least 50%? | CD | CD | CD | CD | CD | CD | CD | CD | CD | CD |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | Yes | No | Yes | Yes | Yes | Yes | Yes | No | No | Yes |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | No | No | No | No | No | Yes | No | Yes | No | No |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | No | No | No | No | No | Yes | No | Yes | No | No |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | Yes | NA | Yes | Yes | Yes | Yes | Yes | Yes | NA | Yes |

| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mausbach et al. (2011) | Mills et al. (2009) | Roepke et al. (2008) | von Kanel et al. (2010) | von Kanel et al. (2010) | von Kanel et al. (2012) | Ho et al. (2014) | von Kanel et al. (2014) | Lucini et al. (2008) | Mausbach et al. (2010) |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10. Was the exposure(s) assessed more than once over time? | No | No | No | No | No | Yes | No | Yes | No | No |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 13. Was loss to follow-up after baseline 20% or less? | NA | NA | NA | NA | NA | Yes | NA | Yes | NA | NA |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

Supplement 1. Quality Appraisal of Included Studies (Continued)

| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mausbach et al. (2012) | Roepke et al. (2011) | Roepke et al. (2012) | Sakurai et al. (2015) | Wu et al. (2017) | Capistrant et al. (2012) | Chattillion et al. (2013) | Cora et al. (2012) | Kring et al. (2010) | Madaleno et al. (2019) |
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Was the participation rate of eligible persons at least 50%? | CD | CD | CD | CD | CD | Yes | CD | CD | CD | Yes |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | No | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | Yes | No | No | No | No | Yes | No | No | No | No |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes | No | No | No | No | Yes | No | No | No | No |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | Yes | NA | Yes | NA | Yes | NA | Yes | Yes | NA | NA |

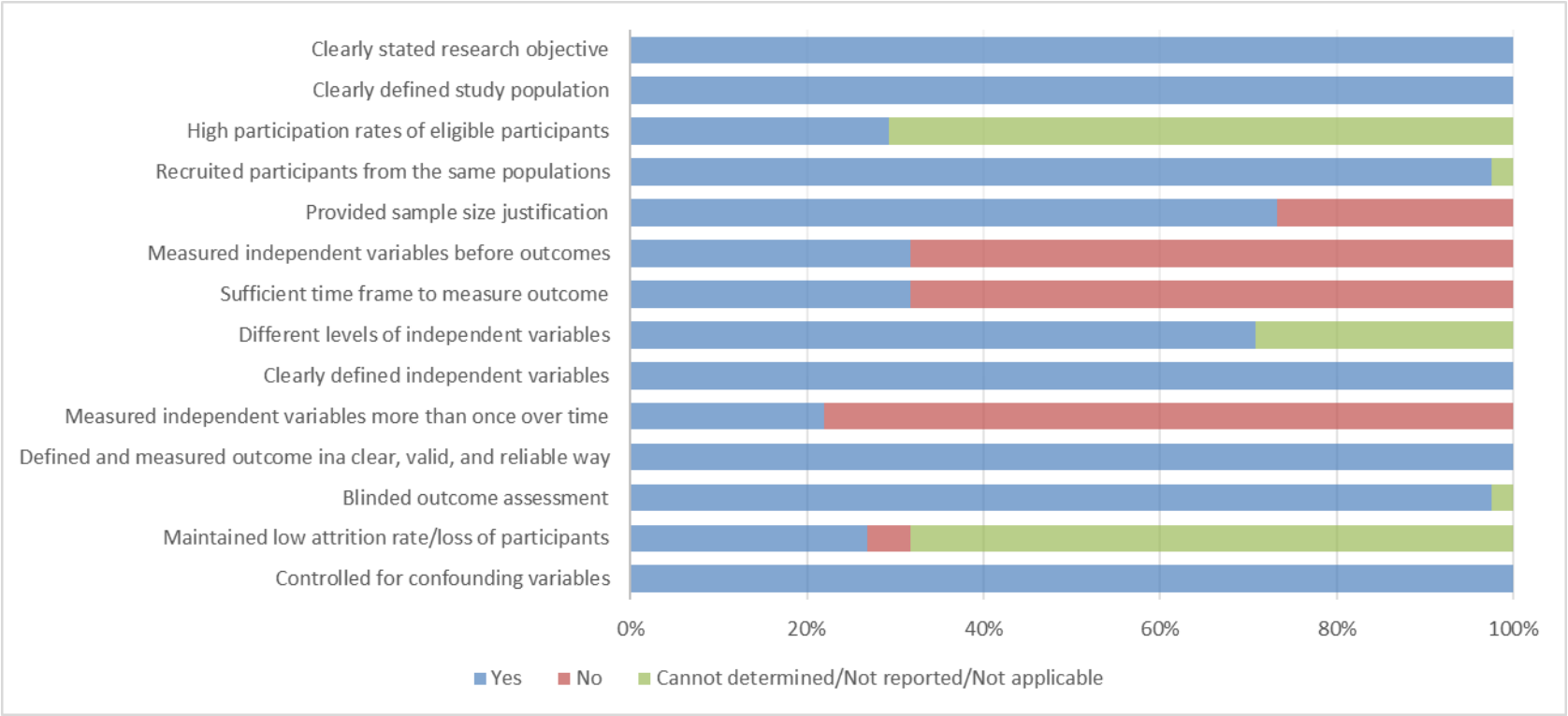
| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mausbach et al. (2012) | Roepke et al. (2011) | Roepke et al. (2012) | Sakurai et al. (2015) | Wu et al. (2017) | Capistrant et al. (2012) | Chattillion et al. (2013) | Cora et al. (2012) | Kring et al. (2010) | Madaleno et al. (2019) |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10. Was the exposure(s) assessed more than once over time? | Yes | No | No | No | No | Yes | No | No | No | No |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | CD | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 13. Was loss to follow-up after baseline 20% or less? | Yes | NA | NA | NA | NA | Yes | NA | NA | NA | NA |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

Supplement 1. Quality Appraisal of Included Studies (Continued)

| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mausbach et al. (2017) | Ross et al. (2017) | Schwartz et al. (2013) | Steel et al. (2019) | Torimoto-Sasai et al. (2015) | Tsukasaki et al. (2008) | von Kanel et al. (2011) | von Kanel et al. (2011) | Haley et al. (2010) | Roepke et al. (2011) | von Kanel et al. (2008) |
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3. Was the participation rate of eligible persons at least 50%? | CD | CD | CD | CD | Yes | CD | Yes | CD | Yes | CD | CD |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | Yes | No | Yes | Yes | Yes | No | Yes | No | No | Yes | Yes |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | Yes | No | No | No | No | No | No | Yes | No | No | No |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes | No | No | No | No | No | No | Yes | No | No | No |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous | Yes | NA | Yes | Yes | NA | Yes | Yes | NA | Yes | Yes | NA |

| Criteria | Yes/No/other (CD, cannot determine; NA, not applicable; NR, not reported) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mausbach et al. (2017) | Ross et al. (2017) | Schwartz et al. (2013) | Steel et al. (2019) | Torimoto-Sasai et al. (2015) | Tsukasaki et al. (2008) | von Kanel et al. (2011) | von Kanel et al. (2011) | Haley et al. (2010) | Roepke et al. (2011) | von Kanel et al. (2008) |
| variable)? | | | | | | | | | | | |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 10. Was the exposure(s) assessed more than once over time? | Yes | No | No | No | No | No | No | Yes | No | No | No |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 13. Was loss to follow-up after baseline 20% or less? | Yes | NA | NA | NA | NA | NA | NA | Yes | NA | NA | NA |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

Supplement 2. Study Quality Appraisal Summary



# Chapter 4: Manuscript Two

## Characterization of Sleep Quality Transitions in Family Caregivers

**Target Journal:** ***International Journal of Behavioral Medicine***

**Authors**

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[4]College of Nursing, University of Kentucky, Lexington, KY

## Abstract

### Background

Family caregivers often report poor sleep quality that is likely worsened by their psychological symptoms. Despite the increasing use of objective measures to track caregivers' sleep over time, sleep patterns have not been explored.

### Objective

To assess short- and long-term patterns of sleep quality states in family caregivers using Markov chain models, and examine the difference in patterns by the levels of psychological symptoms.

### Methods

A total of 33 caregivers who provided in-home care to individuals with chronic illness participated in the study. Depression, anxiety, caregiving stress were assessed using the Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, and Zarit Burden Interview-22, respectively. We collected sleep data for 7 consecutive days using actigraphy. We defined caregivers' sleep efficiency as sleep quality states based on the values < 75%, 75–84%, and ≥ 85% and developed Markov chain models. Using Markov chain transition matrices, we estimated short- and long-term patterns of sleep efficiency and compared the patterns between groups stratified by each psychological symptom.

### Results

Caregivers were most likely to have consistent sleep efficiency state on a night-to-night basis. It required 3.6–5.1 days on average to return to a night of normal sleep efficiency (≥ 85%) from the lower states, and the probability of maintaining normal sleep efficiency in the long run was 42%. Higher probabilities of transitioning to a normal sleep efficiency state were observed in the low depression and anxiety groups compared to the high symptom groups. Differences in the time required to return to a normal state were inconsistent by levels of the symptoms. The long-term probability of maintaining normal sleep efficiency was significantly higher for caregivers with low depression and anxiety compared to the high symptom groups. No differences in the long-term distributions of sleep efficiency were observed in the groups stratified by caregiving stress.

**Conclusion**

Family caregivers' sleep quality largely remains consistent over time and does not recover quickly. Caregivers who experience higher levels of depression and anxiety may be more vulnerable to sustained suboptimal sleep quality levels. Further studies are warranted to assess long-term sleep patterns and examine their impact on health outcomes among caregivers.

**Keywords**: Caregivers, Sleep Quality, Actigraphy, Behavioral Symptoms, Markov Chains

## Introduction

Family caregivers are prone to sleep disturbances such as sleep deprivation and poor sleep quality. Data show that nearly 40% of caregivers have a short sleep duration, less than 7 hours [1], while 30–70% reported poor sleep quality [2–5]. These prevalence rates exceed that in the general population, which is 30-40% [6]. Markers of objective sleep quality, such as sleep efficiency and wake after sleep onset, have increasingly demonstrated reduced sleep quality of caregivers compared with non-caregivers. Caregivers woke up more frequently and stayed awake longer, leading to low sleep efficiency [7,8]. Evidence has shown that poor sleep quality may result in cognitive dysfunction, immunity decline, and cardiovascular disease [9–12].

Depression, anxiety, and caregiving stress are known risk factors for sleep disturbances. Older adult caregivers with high perceived stress demonstrated significantly longer wake after sleep onset than those with low-level stress (82.3 vs. 65.4 minutes) [13]. In caregivers caring for patients with dementia, objective sleep quality such as sleep efficiency and wake after sleep onset and subjective sleep quality were affected by caregiving burden and depression [14]. Alternatively, poor sleep quality reduces the ability to cope with stress and depression, thus generating a circle of escalating symptoms [15].

Homeostatic mechanisms aim to recover sleep following a night of poor sleep [16]. Compensatory behaviors such as increased time in bed may induce sleep variability and disruptive sleep-wake behaviors [17]. Thus, night-to-night variability in sleep patterns is important for understanding an individual's habitual sleep status. The increased availability of wearable monitors that track sleep enables the assessment of habitual sleep patterns and variability in sleep efficiency, duration, and timing in natural settings. However, most investigators report average values of a particular duration limiting investigations on daily variations in sleep parameters. Information on sleep variability may provide new insights into caregivers' sleep status.

Markov chain models may overcome the limitations of traditional statistical analysis in examining sleep patterns. Markov chain modeling explicitly assumes that the current outcome is influenced by past outcomes [18,19], which may enable the description of sleep dynamics over time. The

analysis is known advantageous for its accuracy and simplicity of prediction within and out of sample. Using a set of probabilities that represent transitions between discrete states, the model can predict time-to-event in multiple states and long-term outcomes [20,21]. In the context of healthcare, the modeling has characterized clinical disease progression, behavioral trends, and health status over time [22–24]. Given caregivers' sleep can be easily disrupted for numerous reasons related to their caregiving responsibilities, maintenance of optimal sleep quality throughout a week is difficult. To better understand caregivers' sleep dynamics and patterns, it may be helpful to examine the temporal characteristics of sleep state transitions on a night-to-night basis. Therefore, this study aimed to (1) assess short- and long-term patterns of sleep quality status in family caregivers by developing Markov models, and (2) examine how they differ according to their psychological symptoms.

## Methods

### Participants

This study was approved by the institutional review board of University of Virginia (IRB-HSR 22260). Written informed consent was obtained from all participants prior to study participation. Caregivers were recruited from a community in Central Virginia using study flyers that were distributed to local caregiver support groups and an academic health center; additionally, potential participants were referred by healthcare providers. Inclusion criteria were as follows: Participants were: (1) Aged ≥ 18 years, (2) Primarily responsible for providing care to a family member or friend with a chronic illness in the home, and (3) Not a professional caregiver to the care recipient. Exclusion criteria included (1) formal caregivers to the care-recipients; (2) caregivers of individuals admitted in hospitals or nursing facilities; and (3) night-shift workers. In total, 34 caregivers participated in this study.

### Measures

Demographic variables collected were age, sex, race/ethnicity, sleep medication use, sleep apnea diagnosis, and self-rated general health status (excellent, very good, good, fair, or poor). In this study, sleep quality was modeled as objectively measured sleep efficiency due to its agreed-upon reference values used to categorize sleep quality [25,26]. Psychological symptoms examined were depression,

anxiety, and caregiving stress.

***Sleep Efficiency***

The sleep efficiency of caregivers was assessed using a wrist-worn triaxial accelerometer, ActiGraph GT9X Link (ActiGraph; Pensacola, FL, USA). Actigraphy has shown high reliability compared with polysomnography, the gold standard measure of sleep, and has been widely used and validated to measure sleep parameters [27,28]. Participants were instructed to wear the actigraphy for 24 hours, for 7 consecutive days, except when bathing or performing water sports. Additionally, they were asked to complete a sleep diary during the same period. The vector magnitudes of the three axes were gathered continuously at a sampling rate of 30 Hz and were quantified and stored as absolute activity counts across 1-minute epochs through digital integration. The raw data collected were processed using the manufacturer's software (ActiLife, Version 6.13.4; Pensacola, FL, USA) and were verified for timepoints including bedtimes, wake times, and times when the actigraphy was removed using the sleep diary recorded by each participant. An awake or asleep status was scored in one-minute epochs by applying the Cole–Kripke algorithm [29]. Sleep efficiency was calculated using the software by dividing the number of minutes scored as asleep by the total number of minutes spent in bed.

***Depression***

Depression was assessed using the Patient Health Questionnaire (PHQ)-9, a multipurpose instrument used for screening, diagnosing, monitoring, and measuring depression [30]. The scale scores each item from 0 = "not at all" to 3 = "nearly every day". The PHQ-9 has been validated for use in various settings including primary care [31]. Good internal consistency has been reported with Cronbach's α of 0.85–0.89 and test-retest reliability (intraclass correlation coefficient = 0.92) [30,32]. Cronbach's α in the current study was 0.73. Using a cut-off point (≥ 5) that represents mild to severe depression (vs. minimal symptoms) [30], the variable was dichotomized into low and high depression.

***Anxiety***

Anxiety was measured using the Generalized Anxiety Disorder (GAD)-7, a seven-item instrument used to assess the severity of generalized anxiety disorder [33]. In the GAD-7, participants

self-rate each item based on the severity of symptoms over the past two weeks, on a Likert scale comprising 0 = “not at all,” 1 = “several days,” 2 = “more than half the days,” and 3 = “nearly every day”. This instrument has been validated for primary care patients and the general population [34,35], and has shown high internal consistency with a Cronbach’s α of 0.89–0.92 [33,34]. Cronbach’s α in the current study was 0.83. Using a cut-off point (≥ 5) that represents mild to severe anxiety (vs. minimal symptoms) [33], the variable was dichotomized into low anxiety vs. high anxiety.

***Caregiving Stress***

Caregiving stress was assessed using the 22-item Zarit Burden Interview (ZBI-22) on the caregivers’ health, psychological well-being, finances, social life, and relationship with the patient [36]. Responses were rated on a 5-point Likert scale, ranging from 0 = “never” to 4 = “nearly always”. Scores were summed for a total score of 0–88 with higher scores indicating greater caregiving stress. The scale has shown good internal consistency (Cronbach’s $\alpha = 0.93$), test-rest reliability (intraclass correlation coefficient = 0.89), and construct validity [37–39]. Cronbach’s α in the current study was 0.94. As there is no established cut-off score, the ZBI-22 score was dichotomized into low stress and high stress based on the median value of the sample.

**Markov Chain Model Estimation**

***Markov Chain Modeling***

A Markov chain is a discrete-time stochastic model involving a sequence of observations [40] based on the assumption that one’s future behavior can be predicted based solely on the current state, independent of the past, when discrete behavior is measured at regular intervals [41]. Thus, the probabilities of being in certain states can be determined by the present state that influences the outcomes of the future state. We assumed that: (1) A caregiver exhibits a state of sleep efficiency at 1-day intervals, and (2) The following state transitions can be predicted using the current sleep state alone, not accounting for prior state transition; this represents a first-order Markov chain. Based on these assumptions, we defined: (1) A transition probability matrix for the entire caregiver group, (2) Transition probability matrices stratified by different psychological symptoms, and (3) Short-term transitions and long-term

distribution of sleep efficiency for the entire group and across the stratifications (referred to as mean first-passage time and steady state probabilities, respectively). Analyses were performed using RStudio (version 4.0.2) with the R package *markovchain*.

***State Definition***

Sleep efficiency states were defined for the Markov model using discrete units: < 75% (State 1, S1), 75–84% (State 2, S2), and ≥ 85% (State 3, S3). It is considered that sleep efficiency should be ≥ 85% for optimal health benefits [25,26]. To further discretize the suboptimal levels of sleep efficiency, we used the habitual sleep efficiency scoring criteria of the Pittsburgh Sleep Quality Index (i.e., < 65%, 65–74%, 75–84%, and ≥ 85%) [42]. Subsequently, the category of < 65% was combined with the one of 65–74% due to the very small number of observations. This categorization is aligned with expert consensus regarding sleep efficiency as an appropriate indicator of good sleep quality [43].

***Data Description***

All participants successfully completed the 7-day sleep data collection (average wear time = 98.8%). Of the 34 caregivers who consented to participate in the study, the data from one participant was not valid, therefore, data from 33 caregivers were analyzed. Each participant had a set of seven distinct states (nights 1 to 7); therefore, six transitions per participant occurred at one-day intervals. There were 198 state transitions among the 33 caregivers for 7 days.

***Markov Chain Construction***

We estimated the Markov chain probabilities using maximum likelihood estimation (counting and normalizing the transitions). First, we created a 3 × 3 matrix of transitioning from any sleep state to any other at a one-day interval based on three sleep states (S1, S2, and S3) and nine possible transitions. The rows represented the initial sleep state and the columns represented the next sleep state. For example, given the initial sleep state of S1, there are three possible transitions: S1 to S1, S1 to S2, and S1 to S3. The number of transitions was inserted into each cell. Subsequently, transition probabilities were computed by dividing each cell in the row by the sum of the transition counts for that row, so that the probabilities in a row sum to one. Matrices stratified by psychological symptoms were constructed in

addition to the transition probability matrix for the entire sample.

### *Mean First-Passage Time*

We calculated the mean first-passage times to understand the short-term Markov chain behavior. The mean first-passage time is defined as the mean time to reach a certain state for the first time from each initial state using the transition probability matrix. In this study we computed the number of days required to reach the normal sleep efficiency state (S3) from lower states (S1 and S2).

### Steady State Probabilities

We computed the steady state probabilities that represented the estimated long-term distribution of sleep efficiency states among the entire sample and each psychological symptom group (i.e., depression, anxiety, and caregiving stress). The chi-square test of independence was used to statistically compare the long-term probabilities between the low- and high-symptom groups.

## Results

### Participant Characteristics

The mean caregiver age was 61 years (*SD* = 11.2), and the majority were women (84.8%) and non-Hispanic whites (90.9%) (Table 1). Nearly 40% of the caregivers reported having used a sleep medication during the past month (39.3%), and 18.2% had a sleep apnea diagnosis. Most of them self-rated their health status good, very good, or excellent (87.9%). More than 50% of the participants experienced high depression (69.7%), anxiety (54.5%), or caregiving stress (51.5%). The mean sleep duration for 7 days was 6.8 hours and the mean sleep efficiency was 82.5%. Fifty-two percent of the participants exhibited their mean sleep efficiency below the normal value of 85%.

### Sleep Efficiency in the Entire Group

Caregivers' sleep efficiency was most likely to remain consistent in the same state (Figure 1). The probability of improving towards an optimal sleep efficiency state from the lowest state (S1→S3) was 0.108, whereas that of the intermediate state (S2→S3) was 0.338. Caregivers who exhibited normal sleep efficiency were less likely to have decreased efficiency the following night. The probability of maintaining an optimal sleep state (S3→S3) was 0.632. The mean time required to return to a night of

normal sleep efficiency (≥ 85%) from lower efficiency states (< 75% and 75–85%) was 5.1 and 3.6 days, respectively (Figure 2). The steady state probabilities were 0.190 (S1), 0.393 (S2), and 0.417 (S3).

**Sleep Efficiency in Groups Stratified by Psychological Symptoms**

***Depression***

On any given night, the summed probability of transitioning to the normal sleep efficiency state from the lower states (S1→S3 and S2→S3) and remaining in the normal state (S3→S3) the following night was 1.225 (0 + 0.444 + 0.781) for the low depression group, which was higher than that in the high depression group (0.997 = 0.148 + 0.304 + 0.545) (Figure 3). The time required to transition from the lower states to the normal state (S1→S3 and S2→S3) was 6.4 and 3.1 days, respectively, in the low depression group while it was 4.8 and 3.8 days in the high depression group (Figure 4). The estimated steady state probability of normal sleep efficiency (S3) was higher in the low depression group than in the high depression group (0.562 vs. 0.359) (Table 2). The steady state distributions were significantly different between the two groups ($p = 0.02$).

***Anxiety***

On any given night, the summed probability of transitioning to the normal sleep efficiency state from the lower states (S1→S3 and S2→S3) and remaining in the normal state (S3→S3) the following night was 1.341 (0.105 + 0.476 + 0.760) for the low anxiety group, which was higher than that in the high anxiety group (0.853 = 0.111 + 0.283 + 0.459) (Figure 3). The time required to transition from the lower states to the normal state (S1→S3 and S2→S3) was 4.8 and 2.9 days, respectively, in the low anxiety group while it was 5.3 and 4 days in the high anxiety groups (Figure 4). The estimated steady state probability of normal sleep efficiency (S3) was higher for caregivers with low anxiety than those with high anxiety (0.556 vs. 0.308) (Table 2). The steady state distributions were significantly different between the two groups ($p < 0.001$).

***Caregiving Stress***

On any given night, the summed probabilities of transitioning to the normal sleep efficiency state from the lower states (S1→S3 and S2→S3) and remaining in the normal state the following night were

1.088 (0.056 + 0.389 + 0.643) and 1.069 (0.158 + 0.289 + 0.622) in the low and high stress groups, respectively (Figure 3). The time required to transition from the lower states to the normal state (S1→S3 and S2→S3) was 5.9 and 3.4 days, respectively, in the low stress group while it was 4.7 and 3.8 days in the high stress groups (Figure 4). The estimated steady state probability of normal sleep efficiency (S3) was marginally higher for caregivers with low stress than those with high stress (0.427 vs. 0.399) (Table 2), though the differences in the steady state distributions between the two groups were not statistically significant ($p = 0.56$).

## Discussion

To our knowledge, this is the first study to apply Markov chain modeling to assess the short- and long-term patterns of caregivers' sleep quality status based on its transitions on a night-to-night basis with consecutive 7-day observations. Our findings suggest that caregivers' sleep efficiency is most likely to remain consistent over a week and does not quickly return to the optimal state after a drop in efficiency. Additionally, depression and anxiety may modify the dynamics of sleep quality and the proportions of the optimal sleep state in the long run among caregivers.

Investigators have tracked caregivers' sleep longitudinally and examined changes in sleep status over time based on alterations in their caregiving role, such as care recipients' death or nursing home placement [44,45]. However, sleep quality transitions on a night-to-night basis have not been investigated. This study showed that in participants with lower preceding sleep efficiency, the less likely the sleep states transition to an optimal state. Transitioning from the lowest state of sleep efficiency to a normal state was always least likely to occur in the entire sample and stratified groups. This result suggests that it may be difficult to recover sleep efficiency once a caregiver experiences poor sleep quality and a long time may be required to reach an optimal state. Given the stationary characteristic of suboptimal sleep quality over time, it may be critical to prevent a drop in sleep efficiency and sustained suboptimal sleep quality among caregivers. Continued poor sleep quality in a trajectory within a week is implicated in health problems, such as the prevalence of obesity and hypertension [46]. It is important to describe temporal sleep characteristics and night-to-night patterns in further studies to better understand

the impact of sleep quality variability over the course of a week.

**Depression and Anxiety**

The groups stratified by depression and anxiety levels demonstrated differences in sleep efficiency transition probabilities and steady state distributions. Caregivers with lower depression and anxiety showed greater transitions toward optimal sleep efficiency than those with higher depression and anxiety levels. More than 75% of observed transitions in low symptom groups remained in a normal sleep efficiency state, whereas approximately 50-55% in high symptom groups maintained an optimal sleep efficiency. These observed transition patterns led to significantly lower likelihoods of maintaining an optimal sleep state in the long-run, as displayed in the results of steady state distributions. These differences between groups suggest higher vulnerability to a reduced sleep quality among caregivers with higher levels of depression and anxiety. However, differences in the time required to recover a normal sleep efficiency by the levels of psychological symptoms were inconclusive. Further investigation with a greater number of observations is warranted to understand the short-term patterns by levels of the psychological symptoms.

While there is a scarcity of studies that investigated sleep patterns yet, the adverse impact of depression and anxiety on subjective and objective sleep quality in caregivers is supported by several prior studies [47–50]. Compared to non-depressed and non-anxious caregivers, caregivers with higher levels of depression and anxiety demonstrated greater sleep disturbance scored using the Pittsburgh Sleep Quality Index [49,50]. Low sleep efficiency and high sleep fragmentation derived from actigraphy data were also evident to have significantly independent associations with depression severity among caregivers of patients with dementia [47,48]. Our findings not only support the literature on sleep quality negatively affected by the psychological symptoms but also advance the knowledge by suggesting that depression and anxiety may alter sleep quality dynamics overtime and long-term states. The underlying physiological mechanisms of depression and anxiety with disrupted sleep remain not fully understood; yet, instability in cyclical patterns of shifting between the different sleep stages overnight among depressed individuals, which is likely linked to reduced poor sleep quality, was noted in a previous study

of the general population [51]. Taken together, the current evidence further highlights the need for interventions to improve psychological health while trying to enhance caregivers' sleep quality.

**Caregiving Stress**

Differences in probabilities of transitioning toward a normal sleep efficiency state and, in turn, short- and long-term patterns of sleep efficiency states did not exist between the groups stratified by caregiving stress levels. A possible reason might be the use of median score to divide the sample into two groups, unlike with depression and anxiety, for which validated cutoff points were used. Considering that caregivers in our study reported relatively higher stress compared with that in previous studies [52–54], the median score of caregiving stress might not have been an appropriate cutoff point to differentiate the impact of caregiving stress on sleep patterns. Additionally, the distinction between stress and emotion (depression and anxiety) may explain the discrepancy in the results as stress reflects more cognitive properties, whereas depression and anxiety involve adaptation in response to stressors although these two concepts are interdependent [55]. Further studies exploring the potentially distinct effects of the cognitive and emotional aspects of stress responses on poor quality sleep are warranted.

**Limitations**

This study has several limitations. First, we used a small sample that were derived for Markov chain modeling. Furthermore, the transition probabilities were based on a relatively short horizon of data (one week). There could be further differences in sleep behavior if a longer period is studied. Future research to develop more robust models using larger datasets is warranted to confirm the current finding. Second, the lack of racial and ethnic diversity in the sample may limit the generalizability of the study findings. The study should be replicated in more diverse populations to establish generalizability. Third, we categorized sleep efficiency states using the cutoff points of an established sleep quality questionnaire (the Pittsburgh Sleep Quality Index). However, the cutoff points for suboptimal categories (< 65%, 65–74%, and 75–84%) may lack clinical implications. With stratifications based on clinical evidence of sleep quality parameters, trajectories between states would have more meaningful implications for understanding sleep patterns and identifying target populations for intervention. Lastly, the small sample

size did not allow calculations to take into account for possible confounding factors of sleep efficiency, such as age, smoking, comorbidities, or sleep apnea. Further studies considering these characteristics would provide more insight into the associations between these factors and sleep efficiency patterns.

**Conclusions**

The Markov chain analyses offered new insights to the temporal characteristic of sleep among caregivers. The present findings highlight that objective sleep quality tends to remain in the same state over time with a relatively small extent of recovery, especially if prior sleep state was poor. Additionally, caregivers with high depression/anxiety showed worse sleep patterns, with low probabilities of transitioning into normal sleep efficiency (≥ 85%) and a low long-term probability of maintaining an optimal sleep quality level. Although our study results should be replicated, these suggest different dynamics in sleep quality state by levels of psychological symptoms caregivers experience. To prevent a long-term suboptimal sleep quality level, assessment of sleep trajectories and psychological health may aid to identify groups susceptible to sustained sleep disruption and help them with appropriate resources and education. Moreover, the impact of long-term suboptimal sleep quality on health outcomes among caregivers require further investigation.

**Funding Sources**

This research was supported by the Council for the Advancement of Nursing Science/Southern Nursing Research Society (CANS/SNRS) Dissertation Research Grant.

**Conflict of Interest**

Authors declares no conflict of interest.

**Data Availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**References**

1. Liu Y, Wheaton AG, Edwards VJ, Xu F, Greenlund KJ, Croft JB. Short self-reported sleep duration among caregivers and non-caregivers in 2016. *Sleep Heal.* 2020;6:651–656.

2. Cupidi C, Realmuto S, Lo Coco G, Cinturino A, Talamanca S, Arnao V, et al. Sleep quality in caregivers of patients with Alzheimer's disease and Parkinson's disease and its relationship to quality of life. *Int Psychogeriatr*. 2012;24:1827–1835.

3. Chiu YC, Lee YN, Wang PC, Chang TH, Li CL, Hsu WC, et al. Family caregivers' sleep disturbance and its associations with multilevel stressors when caring for patients with dementia. *Aging Ment Health*. 2014;18:92–101.

4. Lee KC, Yiin JJ, Lin PC, Lu SH. Sleep disturbances and related factors among family caregivers of patients with advanced cancer. *Psychooncology.* 2015;24:1632–1638.

5. Ravyts SG, Dzierzewski JM. Sleep disturbance, mental health symptoms, and quality of life: A structural equation model assessing aspects of caregiver burden. *Clin Gerontol*. 2020;1–10.

6. Dopheide JA. Insomnia overview: Epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. *Am J Manag Care*. 2020;26:S76–84.

7. Dhruva A, Lee K, Paul SM, West C, Dunn L, Dodd M, et al. Sleep-wake circadian activity rhythms and fatigue in family caregivers of oncology patients. *Cancer Nurs.* 2012;35:70–81.

8. Hoyt MA, Mazza MC, Ahmad Z, Darabos K, Applebaum AJ. Sleep quality in young adult informal caregivers: Understanding psychological and biological processes. *Int J Behav Med*. 2021;28:6–13.

9. Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hillier TA, et al. Poor sleep is associated with impaired cognitive function in older women: The Study of Osteoporotic Fractures. *J Gerontol A Biol Sci Med Sci*. 2006;61:405–410.

10. Yan B, Yang J, Zhao B, Fan Y, Wang W, Ma X. Objective sleep efficiency predicts cardiovascular disease in a community population: The Sleep Heart Health Study. *J Am Heart Assoc*. 2021;10:e016201.

11. Irwin MR, Opp MR. Sleep health: Reciprocal regulation of sleep and innate immunity.

*Neuropsychopharmacol*. 2017;42:129–155.

12. Montag SE, Knutson KL, Zee PC, Goldberger JJ, Ng J, Kim KYA, et al. Association of sleep characteristics with cardiovascular and metabolic risk factors in a population sample: The Chicago Area Sleep Study. *Sleep Heal*. 2017;3:107–112.
13. Song Y, Harrison SL, Martin JL, Alessi CA, Ancoli-Israel S, Stone KL, et al. Changes in caregiving status and intensity and sleep characteristics among high and low stressed older women. *J Clin Sleep Med*. 2017;13:1403–1410.
14. Peng HL, Lorenz RA, Chang YP. Factors associated with sleep in family caregivers of individuals with dementia. *Perspect Psychiatr Care*. 2019;55:95–102.
15. Franzen PL, Buysse DJ. Sleep disturbances and depression: Risk relationships for subsequent depression and therapeutic implications. *Dialogues Clin Neurosci*. 2008;10:473–481.
16. Vallières A, Ivers H, Bastien CH, Beaulieu-Bonneau S, Morin CM. Variability and predictability in sleep patterns of chronic insomniacs. *J Sleep Res*. 2005;14:447–453.
17. Buysse DJ, Cheng Y, Germain A, Moul DE, Franzen PL, Fletcher M, et al. Night-to-night sleep variability in older adults with and without chronic insomnia. *Sleep Med*. 2010;11:56–64.
18. Beck JR. Markov models of natural history. *J Clin Epidemiol*. 1988;41:619–621.
19. Sonnenberg FA, Beck JR. Markov models in medical decision making: A practical guide. *Med Decis Mak*. 1993;13:322–338.
20. Efthimiou O, Welton N, Samara M, Leucht S, Salanti G, 4 GWP. A Markov model for longitudinal studies with incomplete dichotomous outcomes. *Pharm Stat*. 2017;16:122–132.
21. Abner EL, Charnigo RJ, Kryscio RJ. Markov chains and semi-Markov models in time-to-event analysis. *J Biom Biostat*. 2013;Suppl 1:19522.
22. Tighe PJ, Bzdega M, Fillingim RB, Rashidi P, Aytug H. Markov chain evaluation of acute postoperative pain transition states. *Pain*. 2016;157:717–728.
23. Tada T, Toyoda H, Kumada T, Kurisu A, Sugiyama A, Akita T, et al. Comparison of liver disease state progression in patients with eradication of versus persistent infection with hepatitis C virus:

Markov chain analysis. *J Viral Hepat*. 2021;28:538–547.

24. Kang Y, Sawyer AM, Griffin PM, Prabhu V V. Modelling adherence behaviour for the treatment of obstructive sleep apnoea. *Eur J Oper Res*. 2016;249:1005–1013.
25. Chen X, Wang R, Zee P, Lutsey PL, Javaheri S, Alcantara C, et al. Racial/ethnic differences in sleep disturbances: The Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep*. 2015;38:877–888.
26. Fung MM, Peters K, Ancoli-Israel S, Redline S, Stone KL, Barrett-Connor E. Total sleep time and other sleep characteristics measured by actigraphy do not predict incident hypertension in a cohort of community-dwelling older men. *J Clin Sleep Med*. 2013;9:585–591.
27. Mantua J, Gravel N, Spencer RMC. Reliability of sleep measures from four personal health monitoring devices compared to research-based cctigraphy and polysomnography. *Sensors (Basel)*. 2016;16:646.
28. Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen JM, Solet JM, et al. Measuring sleep: Accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. *Sleep.* 2013;36:1747–1755.
29. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. *Sleep*. 1992;15:461–469.
30. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613.
31. Cameron IM, Crawford JR, Lawton K, Reid IC. Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care. *Br J Gen Pract*. 2008;58:32–36.
32. Gelaye B, Williams MA, Lemma S, Deyessa N, Bahretibeb Y, Shibre T, et al. Validity of the patient health questionnaire-9 for depression screening and diagnosis in East Africa. *Psychiatry Res*. 2013;210:653–661.
33. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med*. 2006;166:1092–1097.
34. Löwe B, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, et al. Validation and

standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. *Med Care*. 2008;46:266–274.

35. Ruiz MA, Zamorano E, García-Campayo J, Pardo A, Freire O, Rejas J. Validity of the GAD-7 scale as an outcome measure of disability in patients with generalized anxiety disorders in primary care. *J Affect Disord*. 2011;128:277–86.
36. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: Correlates of feelings of burden. *Gerontologist*. 1980;20:649–655.
37. Schreiner AS, Morimoto T, Arai Y, Zarit S. Assessing family caregiver's mental health using a statistically derived cut-off score for the Zarit Burden Interview. *Aging Ment Health*. 2006;10:107–111.
38. Al-Rawashdeh SY, Lennie TA, Chung ML. Psychometrics of the Zarit Burden Interview in caregivers of patients with heart failure. *J Cardiovasc Nurs*. 2016;31:E21–28.
39. Seng BK, Luo N, Ng WY, Lim J, Chionh HL, Goh J, et al. Validity and reliability of the Zarit Burden Interview in assessing caregiving burden. *Ann Acad Med*. 2010;39:758–763.
40. Kendall DG. Stochastic processes occurring in the theory of queues and their analysis by the method of the imbedded Markov chain. *Ann Math Stat.* 1953;24:338–354.
41. Beck JR, Pauker SG. The markov process in medical prognosis. *Med Decis Mak*. 1983;3:419–458.
42. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213.
43. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's updated sleep duration recommendations: Final report. *Sleep Heal*. 2015;1:233–243.
44. von Känel R, Mausbach BT, Ancoli-Israel S, Dimsdale JE, Mills PJ, Patterson TL, et al. Sleep in spousal Alzheimer caregivers: A longitudinal study with a focus on the effects of major patient transitions on sleep. *Sleep*. 2012;35:247–255.
45. von Kanel R, Mausbach BT, Mills PJ, Dimsdale JE, Patterson TL, Ancoli-Israel S, et al. Longitudinal

relationship of low leisure satisfaction but not depressive symptoms with systemic low-grade inflammation in dementia caregivers. *J Gerontol B Psychol Sci Soc Sci*. 2014;69:397–407.

46. Chen J, Patel SR, Redline S, Durazo-Arvizu R, Garside DB, Reid KJ, et al. Weekly sleep trajectories and their associations with obesity and hypertension in the Hispanic/Latino population. *Sleep*. 2018;41:zsy150.
47. Smagula SF, Krafty RT, Taylor BJ, Martire LM, Schulz R, Hall MH. Rest-activity rhythm and sleep characteristics associated with depression symptom severity in strained dementia caregivers. *J Sleep Res.* 2017;26:718–725.
48. Beaudreau SA, Spira AP, Gray HL, Long J, Rothkopf M, Gallagher-Thompson D. The relationship between objectively measured sleep disturbance and dementia family caregiver distress and burden. *J Geriatr Psychiatry Neurol*. 2008;21:159–165.
49. Mo Y, Lai X, Li L, Lu Y zhen. Sleep, depression, and anxiety in family caregivers of nasopharyngeal carcinoma patients before therapy. *Acta Psychol (Amst)*. 2022;223:103504.
50. Smyth A, Whitehead L, Quigley E, Vafeas C, Emery L. Disrupted sleep and associated factors in Australian dementia caregivers: A cross-sectional study. *BMC Geriatr*. 2020;20:312.
51. Elovainio M, Lipsanen J, Halonen R, Kuula L, Räikkönen K, Pesonen A-K. Is moderate depression associated with sleep stage architecture in adolescence? Testing the stage type associations using network and transition probability approaches. *Psychol Med*. 2021;51:426–434.
52. Higginson IJ, Gao W, Jackson D, Murray J, Harding R. Short-form Zarit Caregiver Burden Interviews were valid in advanced conditions. *J Clin Epidemiol*. 2010;63:535–542.
53. Al-Rawashdeh SY, Lennie TA, Chung ML. The association of sleep disturbances with quality of life in heart failure patient-caregiver dyads. *West J Nurs Res*. 2017;39:492–506.
54. Brodaty H, Woodward M, Boundy K, Ames D, Balshaw R. Prevalence and predictors of burden in caregivers of people with dementia. *Am J Geriatr psychiatry*. 2014;22:756–65.
55. Lazarus RS. *Stress and emotion: A new synthesis.* New York, NY: Springer Publishing; 2006.

**Table 1** Participant characteristics (N=33)

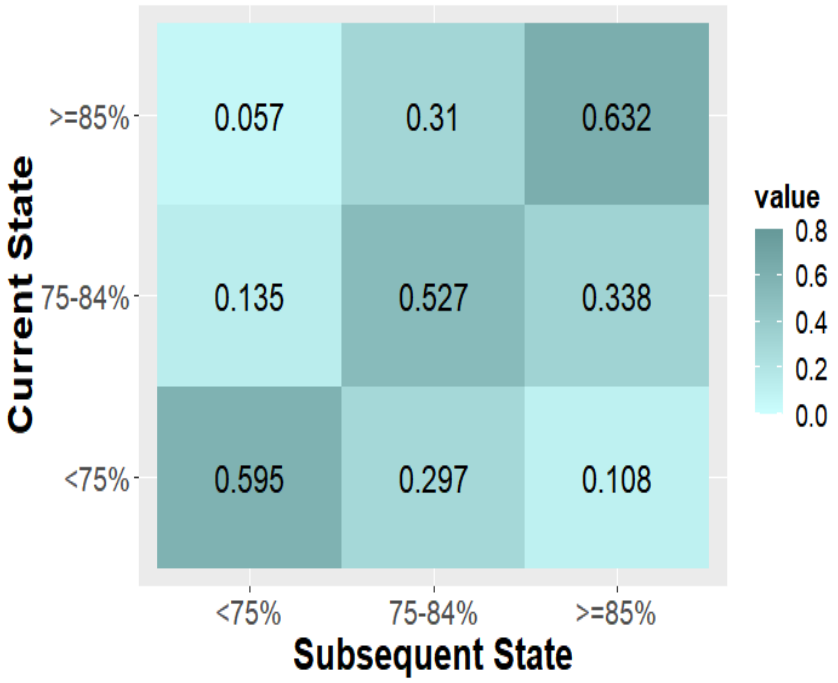
| | | n (%) | Mean (*SD*) |
|---|---|---|---|
| Age (years) | | | 61.27 (11.24) |
| Sex | Male | 5 (15.2) | |
| | Female | 28 (84.8) | |
| Race/ethnicity | Non-Hispanic white | 30 (90.9) | |
| | Asian | 2 (6.1) | |
| | Hispanic | 1 (3.0) | |
| Sleep medication use | Yes | 13 (39.3) | |
| | No | 20 (60.7) | |
| Sleep apnea diagnosis | Yes | 6 (18.2) | |
| | No | 27 (81.8) | |
| General health status | Excellent | 5 (15.2) | |
| | Very good | 11 (33.3) | |
| | Good | 13 (39.4) | |
| | Fair | 4 (12.1) | |
| | Poor | 0 (0.0) | |
| Depression | | | 6.36 (3.82) |
| | High (≥ 5) | 23 (69.7) | |
| | Low (< 5) | 10 (30.3) | |
| Anxiety | | | 5.21 (3.96) |
| | High (≥ 5) | 18 (54.5) | |
| | Low (< 5) | 15 (45.5) | |
| Caregiving stress | | | 38.88 (17.74) |
| | High (≥ 39) | 17 (51.5) | |
| | Low (< 39) | 16 (48.5) | |
| Mean sleep duration in hours | | | 6.81 (0.86) |
| Mean sleep efficiency | | | 82.52 (6.99) |
| | < 75% | 6 (18.2) | |
| | 75–84% | 11 (33.3) | |
| | ≥ 85% | 16 (48.5) | |

**Table 2** Steady states according to psychological symptoms

| | Low Symptom | | | High Symptom | | | $p^*$ |
|---|---|---|---|---|---|---|---|
| | < 75% (S1) | 75–84% (S2) | ≥ 85% (S3) | < 75% (S1) | 75–84% (S2) | ≥ 85% (S3) | |
| Depression | 0.161 | 0.277 | 0.562 | 0.200 | 0.440 | 0.359 | **0.02** |
| Anxiety | 0.211 | 0.233 | 0.556 | 0.170 | 0.522 | 0.308 | **< 0.001** |
| Caregiving Stress | 0.212 | 0.362 | 0.427 | 0.175 | 0.426 | 0.399 | 0.56 |

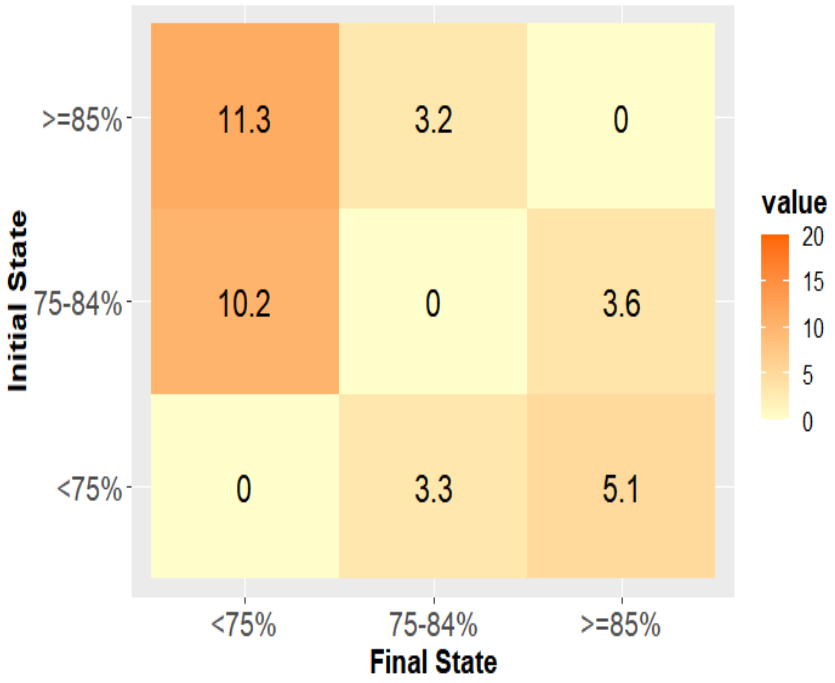
*P values for Chi-square independent tests.

**Fig. 1** Sleep efficiency state transition probability matrix



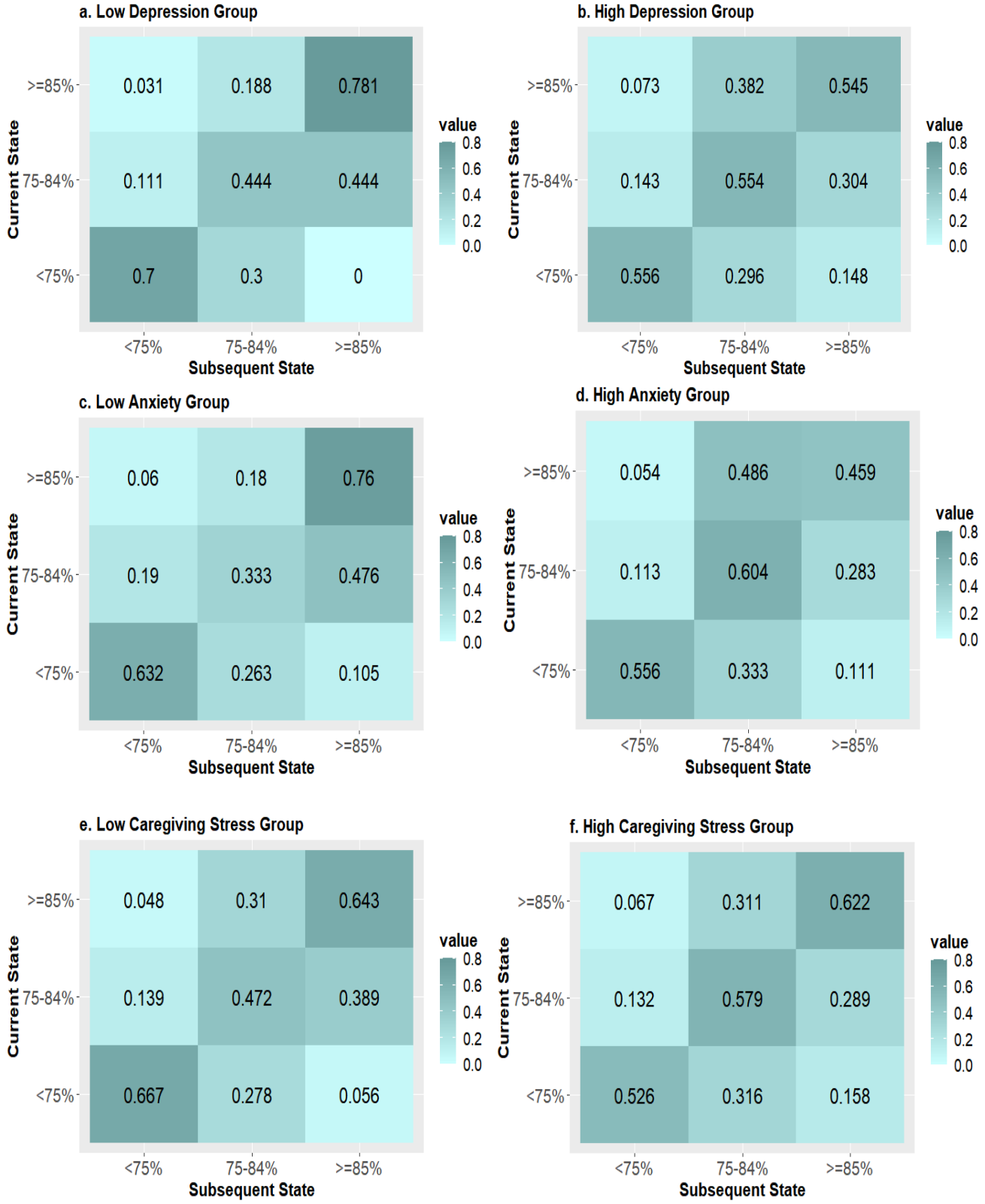

*Note*. Each cell represents a probability of transitioning from a current sleep efficiency state (rows) to the subsequent sleep efficiency state (columns). The darker cell, the higher probability. For example, the cell in the second row and the third column shows a 34% of probability of transitioning for the current state of 75-84% to the state of ≥ 85% the following night.

**Fig. 2** Mean first-passage time of sleep efficiency states



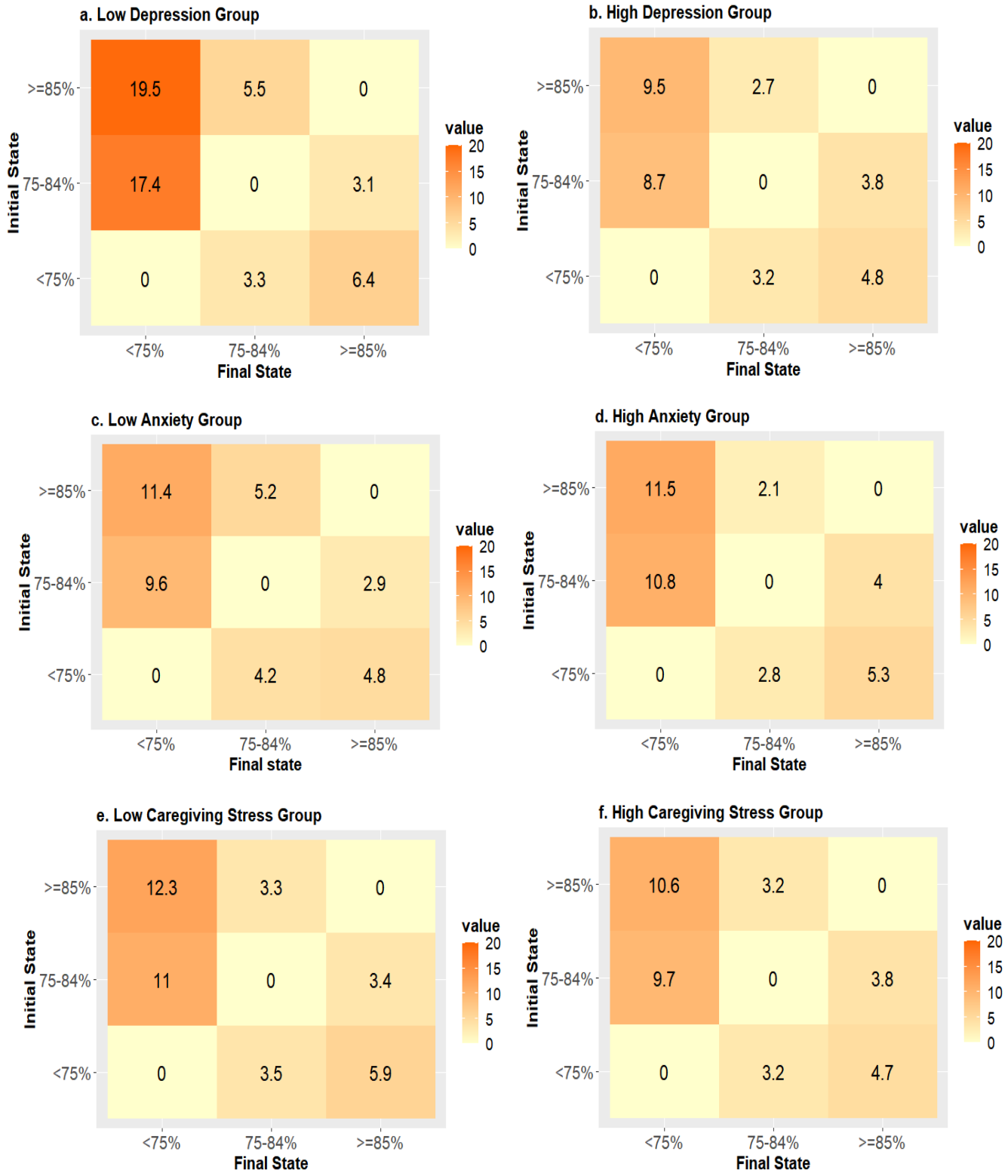

*Note*. Mean first-passage time means the length of time (days) required to reach each possible final sleep efficiency state (columns) from each possible initial state (rows) for the first time. The darker cell, the greater length of time required. The length of time required to reach the same state (numbers in the diagonal) was not computed. For example, 5.1 days takes to reach a final state of ≥ 85% from an initial state of < 75%.

**Fig. 3** Sleep efficiency state transition probability matrices of groups stratified by psychological symptoms



*Note***.** Transition matrices were separately created for groups stratified by levels of each psychological symptom: a & b for caregivers with high/low depression; c & d for caregivers with high/low anxiety; e & f for caregivers with high/low caregiving stress.

**Fig. 4** Mean first-passage time of sleep efficiency states according to psychological symptoms (days)



*Note*. The length of time required to reach each possible final state from an initial state was separately calculated for groups stratified by each psychological symptom: a & b for caregivers with high/low depression; c & d for caregivers with high/low anxiety; e & f for caregivers with high/low caregiving stress.

# Chapter 5: Manuscript Three

## Association of Disrupted Sleep with 24-Hour Blood Pressure Variability in Caregivers of Patients with Chronic Illness

**Target Journal:** ***Journal of Psychosomatic Research***

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## Abstract

### Introduction

A growing body of research shows an association between caregiving and increased cardiovascular disease (CVD) risk. Blood pressure variability (BPV) is known as a surrogate marker of CVD development. However, BPV in caregivers has rarely been used to assess for CVD risk, especially in relation to psychological and behavioral factors. The purpose of this study was to examine the associations of psychological symptoms (i.e., caregiving stress and depressive symptoms) and sleep quality with 24-hour BPV among caregivers of individuals with chronic illness.

### Methods

Thirty caregivers (25 female; 27 non-Hispanic white; mean age 62 years) who provided in-home care were recruited from the community in this cross-sectional study. Caregiver demographic data, caregiving stress (Zarit Burden Interview), and depressive symptoms (Patient Health Questionnaire-9) were obtained. Sleep quality (i.e., sleep efficiency, wake after sleep onset, the number of awakenings) was assessed using an actigraph for 7 consecutive days. Systolic and diastolic BPV over 24 hours, while awake (daytime), and while sleeping (night time) were obtained by ambulatory BP monitoring. Pearson's correlations and multiple linear regression were conducted to examine associations of psychological symptoms and sleep quality with BPV.

### Results

Sleep efficiency was negatively correlated with diastolic BPV while awake ($r$ = -0.368, $p$ = 0.045). The number of awakenings during sleep was positively correlated with systolic BPV while awake ($r$ = 0.426, $p$ = 0.019) and diastolic BPV while awake ($r$ = 0.422, $p$ = 0.020). Caregiving stress and depression were not correlated with BPV. After controlling for age and mean arterial pressure, the number of awakenings was associated with increased systolic BPV over 24 hours ($B$ = 0.194, $p$ = 0.018) and systolic BPV while awake ($B$ = 0.280, $p$ = 0.002), respectively.

### Conclusion

Caregivers' disrupted sleep represented by frequent awakenings may play a role in increased CVD risk as

evidenced by increased BPV. While future large clinical studies should be conducted to confirm these findings, improving sleep quality would need to be considered for CVD prevention strategies for caregivers.

**Keywords**: Caregivers, Cardiovascular Diseases, Heart Disease Risk Factors, Behavioral Symptoms, Sleep Quality

## 1. Introduction

According to a 2020 report by the National Alliance for Caregiving, nearly one-fifth of American adults (53 million) are providing unpaid, informal care to their loved ones with chronic illness or disabilities [1]. It is well documented that caregiving demands are likely to adversely affect caregivers' health [2–5]. Among physical health problems that caregivers are known to be susceptible to, increased cardiovascular disease (CVD) risk has been supported by a growing body of research that demonstrated caregivers' higher incidence of CVD compared to non-caregivers [6–9].

Various psychological and behavioral factors are associated with cardiovascular health. Psychological symptoms including caregiving stress and depression may increase risk of incident hypertension and CVD [10–12]. Behavioral factors, such as disturbed sleep due to caregiving has the potential to place caregivers at increased risk for developing myocardial infarction and other CVD [13–15]. The mechanism by which psychological symptoms and disturbed sleep potentially increase CVD risk is not clear. Yet, it is plausible that these factors may alter autonomic and hemodynamic regulation along with provoking inflammatory responses and endothelial dysfunction [16,17].

Subclinical CVD markers that are considered fundamental precursors to CVD, such as arterial stiffness and carotid intima-media thickness, have been studied to assess ability to identify those at high CVD risk and support primary CVD prevention [18–20]. Blood pressure variability (BPV) is one such subclinical CVD marker and is defined as blood pressure (BP) that oscillates within individuals in response to hemodynamic, humoral, behavioral, and environmental factors to maintain homeostasis [21]. Sustained excessive BPV is indicative of alterations in hemodynamic systems or pathological conditions that can hamper cardiovascular homeostasis [22]. Of several types of BPV, short-term BPV is defined as circadian modulations in BP over a 24-hour period, and reflects sympathetic activation and arterial compliance [22]. A large number of studies demonstrate that increased BPV independently predicts the CVD development and cardiovascular/all-cause mortality in both hypertensive and normotensive populations [23–27]; yet, caregiver BPV has not been described despite the potential prognostic significance for CVD development.

The associations among caregiver BPV with psychological symptoms and sleep may provide clues to understand the early hemodynamic changes of CVD resulting from caregiving burden. Describing these relationships will also inform strategies for CVD prevention in caregivers. Therefore, the purpose of this pilot study was to examine the associations of 24-hour BPV with psychological and behavioral factors in caregivers who took care of adults with chronic illness. We hypothesized that high psychological symptoms (i.e., caregiving stress and depression) and low objectively measured sleep quality (i.e., sleep efficiency, wake after sleep onset [WASO], and the number of awakenings) are independent predictors of increased 24-hour BPV.

## 2. Methods

### 2.1. Sample

This study was a cross-sectional descriptive study. We recruited adults aged 18 years or older who identified as a primary caregiver to a family member or friend with chronic illness. Eligible participants were required to: (1) be primarily responsible for providing in-home care and personal assistance to an adult family member or friend with chronic illness; and (2) have no major health conditions such as cancer and cardiac conditions. Exclusion criteria included (1) professional caregivers to the care-recipients; (2) caregivers of patients admitted in hospitals, nursing skilled facilities, or nursing homes; and (3) night-shift workers.

### 2.2. Procedure

The study protocol was approved by the institutional review board of University of Virginia (IRB-HSR 22260). Participants were recruited through study flyers and advertisements posted at an academic medical center, on its clinical trial website, in a local newspaper, and distributed to local caregiver support groups. Caregivers were also referred by healthcare providers or past participants. After eligibility screening was conducted, we asked eligible participants to select a week for study participation that would be representative of their daily life in terms of activities and caregiving tasks. Study visits for participants were scheduled between 8 am to 11 am to minimize the variation potentially confounded by a

circadian pattern of the cardiovascular system. After informed and written consent, we collected participants' demographic, health-related, and caregiving-related information through questionnaires and then conducted assessment for height, weight, and an office BP. Height and weight for calculating body mass index (BMI) were measured using a wall mounted stadiometer and electronic scale. After the participant had been in the supine position for 10 minutes, a trained researcher measured BP twice in a non-dominant arm separated by 2 minutes using the Omron 3 Series Upper Arm Blood Pressure Monitor (Omron, Japan). The mean BP value was recorded as an office BP. Next, we applied an actigraphy device to the participant's non-dominant wrist for 7-day-sleep/activity tracking and instructed them to complete a daily sleep diary. Participants recorded their time in bed/out of bed and times when the actigraphy was not worn in the diary. We also applied an ambulatory BP monitor to the participant's non-dominant arm for a twenty-four-hour (24-h) assessment. Participants returned the devices and sleep diary in 7 days.

**2.3. Measures**

We measured demographics, health-related factors, caregiving characteristics, psychological symptoms (caregiving stress and depression), objective sleep quality, and 24-hour BPV. Demographics included age, sex, race/ethnicity, and health-related factors were smoking status, BMI, office mean arterial pressure (MAP), the diagnosis of sleep apnea and diabetes, and the use of antihypertensive and cholesterol medications. Caregiving characteristics included the relationship with the care-recipient (spouse, adult child, parent, or relative/friend), the number of care-recipient's health conditions (single or multiple conditions), caregiving hours per week ($< 20$ hours or $\geq 20$ hours), and caregiving duration ($< 3$ years or $\geq 3$ years). All the caregiver characteristics, except BMI and office MAP, were self-reported.

**2.3.1. Caregiving stress**

Caregiving stress was measured with the widely used 22-item Zarit Burden Interview (ZBI) instrument for measuring the level of caregiving stress [28]. The questions focus on caregiver health, psychological well-being, finances, social life, and the relationship between the caregiver and the patient. Responses to the 22 items are on a 5-point Likert scale ranging from 0 (never) to 4 (nearly always). The

overall score ranges from 0 to 88 and is generated by adding up each item score with higher scores indicating greater caregiving stress. Cut-off points for ZBI-22 are not established; yet, the developer proposed considering the burden moderate to severe for scores ≥ 41 [29]. The ZBI scale has shown good reliability and validity across caregiver populations [30–32].

**2.3.2. Depressive symptoms**

The Patient Health Questionnaire (PHQ)-9 was used to assess for depression. The PHQ-9 is an instrument designed to diagnose depressive disorder and grade depressive symptom severity [33]. The scale assesses nine depressive symptoms and each item can be scored from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27, and depressive symptoms are considered mild to severe for scores ≥ 5 [33]. The PHQ-9 has been validated for use in various settings and populations, including primary care [34,35]. Good reliability has been reported with Cronbach's α ranging from 0.85-0.89 [33,36].

**2.3.3. Sleep quality**

Sleep quality parameters including sleep efficiency, WASO, and the frequency of awakenings were assessed using data obtained by an ActiGraph GT9X Link (ActiGraph; Pensacola, FL, USA) which is a small and lightweight triaxial wrist accelerometer. Actigraphy has been compared against polysomnography, the gold standard for assessing sleep, and shown to be reliable and valid [37,38]. The actigraphy monitor (ActiGraph) has frequently been used and validated in healthy community-dwelling individuals for assessing sleep status [39–41]. The actigraphy device was worn for 7 consecutive days on a participants' non-dominant wrist except during bathing or swimming. Collected raw acceleration data were processed using the manufacturer's software (ActiLife, Version 6.13.4; Pensacola, FL, USA) and validated by the participant sleep diary. The software filtered the raw data and summed into 1-minute epochs that were converted to activity counts. Sleep from wake times was determined by validated minute-by-minute scoring of the Cole-Kripke algorithm [42]. Sleep data of the first day when 24-h BP monitoring was being conducted were excluded for analysis due to a potential confounding effect of BP measurement on sleep quality during the night. Sleep quality parameters that we assessed included: (1)

sleep efficiency defined as the ratio of the number of sleep minutes (sleep duration) to the total number of minutes spent in bed; (2) WASO defined as the total number of minutes that the participant was awake after sleep onset occurred; (3) frequency of awakenings defined as the number of awakening episodes between the sleep onset and sleep offset.

**2.3.4. 24-hour blood pressure variability**

Ambulatory BP was recorded for a 24-h period at 1-h intervals by means of a validated BP measurement device (Spacelabs 90227; SpaceLabs Healthcare, Washington, USA). Appropriate cuff sizes for the participants' upper arms were used according to the American Heart Association guidelines for BP measurement [43]. The arm cuff was positioned on the non-dominant side. The participants were instructed to maintain their normal daily activities but keep the arm extended and immobile at the time of cuff inflation. Recorded readings of BP were downloaded from the monitor into the custom software (Sentinel 11, SpaceLabs Healthcare, Washington, USA). Daytime (awake) and night-time (sleep) intervals were defined individually based on participants' sleep diaries. Recordings that included at least 70% of valid readings per participant throughout the 24-h period were considered sufficient quality and included in the analysis [44].

As an index of BPV, we computed successive variation (SV) [45] for 24-h, awake time, and sleep time. The SV accounts for the average of the squared difference between consecutive BP measurements. Compared to the index of standard deviation and coefficient of variation, the SV addresses the time sequence of measurements [46] and removes the influence from the superimposed circadian BP variation [47]. The parameter is calculated using the following formula where *n* denotes the number of valid BP readings and *k* is the order of readings: $SV = \sqrt{(1/(n-1)\ \sum_{k=1}^{n-1}(BP_{k+1} - BP_k)^2}$.

**2.4. Data analysis**

Data were summarized using the means (SD) or frequencies (percentages) where appropriate. Bivariate correlations were assessed among participant characteristics, psychological symptoms, sleep quality, and BPV, using two-tailed Pearson's correlation coefficients. Multiple linear regression analyses

were performed to examine the associations of the psychological symptoms and sleep quality with BPV while controlling for covariates. Along with age and MAP that are well-known risk factor of BPV, potential predictors that were significantly correlated with BPV were included in the regression analysis. Due to high correlations among the sleep quality parameters, each sleep variable was included in a separate model. All assumptions for linear regression (i.e., normality, linearity, homoscedasticity, and absence of multicollinearity) were tested. A *p*-value of $< 0.05$ was considered significant and all statistical analyses were conducted using IBM SPSS Statistics software (version 26.0).

## 3. Results

### 3.1. Sample characteristics

Of 34 caregivers who completed study participation, four participants were excluded from the analytic sample due to their invalid data of the main variables of interest (sleep or BPV). Thus, a total of 30 caregivers were included in the sample for this study (Table 1). The mean age of caregivers was 62 years (*SD* = 11.6) and the majority were female (83.3%) and non-Hispanic white (90.0%). Seventy percent reported having never used cigarettes, and mean BMI was 28.3kg/m$^2$ (*SD* = 5.4). One fifth of caregivers were diagnosed with sleep apnea, and 10% with type 2 diabetes. Some reported taking medications for hypertension (23.3%) or high cholesterol (26.7%). Most participants (60.0%) were caring for a spouse living with chronic illness, and the majority of care recipients (70%) had two or more health conditions. More than half of the caregivers spent 20 or more hours per week providing care (66.7%) and have taken the caregiving role for 3 years or longer (56.7%).

### 3.2. Caregiving stress, depression, and sleep quality

The mean scores of caregiving stress (ZBI-22) and depression (PHQ-9) were 37.3 (*SD* = 17.8) and 6.0 (*SD* = 3.8). One third of caregivers fell into a moderate to severe caregiving stress group, and 67% reported at least mild depressive symptoms. Cronbach's α for stress and depression were 0.94, 0.73 respectively. Participants' sleep duration at average was 6.8 hours (*SD* = 0.9) per night. The mean sleep efficiency was 82.8% (*SD* = 6.6), which is below the optimal status (≥ 85%). The mean WASO was 80.9

minutes (*SD* = 42.6) that account for 19.8% of the sleep duration, and the mean number of awakenings per night was 21 (*SD* = 7.4). There were no correlations between each psychological symptom and sleep quality parameter (Supplementary Table 1).

### 3.3. 24-hour blood pressure variability

Participants' office mean systolic/diastolic BP was 122/74 mmHg. The mean BP-awake was 123/73mmHg and the mean BP-sleep was 110/64mmHg. The mean systolic and diastolic SV-24h was 13.07 (*SD* = 3.34)/9.39 (*SD* = 2.18), mean SV-awake was 13.67 (*SD* = 3.92)/9.11 (*SD* = 2.46), and mean SV-sleep was 12.60 (*SD* = 4.94)/10.31 (*SD* = 3.76).

Pearson's coefficients revealed that participants' characteristics and psychological factors (i.e., caregiving stress, depression) were not correlated with SVs, while MAP was positively correlated with systolic SV-awake (Table 2). Sleep efficiency was negatively correlated with diastolic SV-awake ($r$ = -0.368, $p$ = 0.045). The number of awakenings during sleep was positively correlated with systolic SV-awake ($r$ = 0.426, $p$ = 0.019) and diastolic SV-awake ($r$ = 0.422, $p$ = 0.020).

Preliminary analysis of associations among the independent variables included in a regression model (i.e., a sleep parameter, age, and MAP) revealed that there was no presence of multicollinearity (VIF values < 10). Controlling for age and MAP, the number of awakenings was significantly associated with systolic SV-24h ($B$ = 0.194, $p$ = 0.018) and systolic SV-awake ($B$ = 0.280, $p$ = 0.002) in each regression model (F (3, 26) = 3.841, $p$ = 0.021, $R^2$ = 0.307; F (3, 26) = 7.042, $p$ = 0.001, $R^2$= 0.448, respectively) (Table 3). That is, an awakening was associated with an increase of 0.194 unit in systolic SV-24h and of 0.280 unit in systolic SV-awake, respectively. The number of awakenings was not associated with systolic SV-sleep or diastolic SVs (Table 3), and sleep efficiency was not associated with any SVs when the covariates were taken into account (Supplementary Table 2).

## 4. Discussion

Results from this pilot study provided partial support for our hypotheses among family caregivers of community-dwelling patients with chronic illness. We observed that objective sleep quality as

represented by the number of nighttime awakenings was an independent predictor of increased short-term BPV over 24 hours and awake time while caregiving stress and depression were not correlated with BPV. The present finding adds to the literature suggesting that caregiver disrupted sleep may be linked to increased BPV.

Our findings are similar to previous data. While no investigators have examined the association between caregivers' sleep quality and BPV, the impact of objectively measured severity of sleep apnea or sleep quality has been related to suboptimal BP patterns in the general population. In a study including 384 participants with the mean age of 50 years, individuals with obstructive sleep apnea associated with frequent arousals from sleep by the occluded airway had higher 24-h, daytime, and nighttime systolic BPV than those without [48]. In another study of 78 healthy middle-aged adults, objective sleep quality represented by actigraphy-measured sleep efficiency was an independent predictor of higher systolic BPV-24h [49]. Our study found that sleep efficiency along with WASO that indicates overall sleep quality were not associated with BPV. Rather, the number of awakenings that reflects frequent and brief episodes of wakefulness [50] was an independent predictor of systolic BPV.

The link between disrupted sleep represented by frequent awakenings and excessive BPV remains unclear; yet, impaired autonomic function and arterial compliance may be implicated. Augmented sympathetic nervous system activities caused by disrupted sleep may increase BP and the hemodynamic change can further lead to endothelial dysfunction by exerting greater arterial wall stress [51]. In studies of spousal caregivers of individuals with Alzheimer's disease, poor sleep quality with high disruption or low sleep efficiency was linked to elevated D-dimer, interleukin-6, and atherosclerotic risk [13,14]. These biomarkers represent coagulation, inflammation, and atherosclerosis, all of which are related to arterial compliance [52,53]. In a broad sense, autonomic dysfunction and compromised arterial compliance that may impair baroreflex function may be a link between poor quality sleep and altered BP regulation [54,55]. However, further studies are needed to better understand subclinical CVD mechanisms in relation to sleep quality.

While levels of arterial BP are critical for CVD prevention, numerous studies have demonstrated

that BPV is a significant predictor of CVD events, independent of average BP levels in hypertensive and in the general population [56–61]. In the current study, the number of awakenings were not correlated with office BP, mean 24-h BP, or mean awake-time BP levels. Moreover, the frequency of awakenings was associated with systolic BPV-24h and systolic BPV-awake while adjusting for MAP. This suggests that short-term BPV may be a more sensitive marker than absolute levels of BP in detecting adverse impacts of poor sleep quality on BP regulation.

Contrary to our hypothesis that caregiving stress and depression would predict increased BPV, the association of either caregiving stress or depression with BPV was not observed. The small sample size might have limited statistical power for detecting the association. Further, this may reflect a protective cardiovascular response to chronic life stress or depressive mood in this healthy sample. In a prior study in mice, acute stress produced increased BPV that was associated with the sympathetic activity and impaired baroreflex control, whereas chronic stress led to reduced BPV [62]. This distinction was explained by a notion that chronic stress may induce a rebound increase of endothelial nitric oxide (NO), a potent vasodilator, in response to increased sympathetic activities [62]. Future studies on the roles of acute and chronic stress in BP regulation may increase understanding of the CVD risk magnitude that may change over the course of caregiving experience.

**Limitations**

Our results should be interpreted in light of the study design and sample limitations. First, this pilot study was limited by a small convenience sample. Given our white-dominant participants, the association between sleep quality and BPV should be confirmed in a larger sample with diversity in race/ethnicity. A larger sample size would also allow other potential confounding factors of CVD risk, such as comorbidity and health behavior, to be included as covariates. Second, an inherent limitation of a cross-sectional design prevented inferring directionality between poor sleep quality and short-term BPV. A prospective study is necessary to confirm the impact of disturbed sleep on BP dynamics. Third, we requested participants to select a typical week for study participation, yet daily routines may not have been typical in relation to caregiving tasks and sleep status. Also, some stressful events or the daily

pattern of activities of the participants that we did not take into account might have affected BP readings.

In conclusion, we assessed caregiver CVD risk through short-term BPV and examine the associations of BPV with caregivers' psychological symptoms and objectively measured sleep quality. The finding of this pilot study adds support to prior research suggesting that caregivers' disrupted sleep may have an adverse impact on autonomic function and arterial compliance that could be represented by increased BPV. The subclinical markers such as BPV may have the potential to help identify subgroups of caregivers in more need of support for mitigating detrimental consequences of caregiving on CVD risk. This study also provides evidence that supports the importance of sleep quality assessment addressed in the current published guidelines on the primary prevention of CVD [63]. Assessing sleep barriers and sleep status among caregivers followed by appropriate support will be critical for CVD prevention in this population.

**Funding Sources**

This research was supported by the Council for the Advancement of Nursing Science/Southern Nursing Research Society (CANS/SNRS) Dissertation Research Grant.

**Conflict of Interest**

Authors declares no conflict of interest.

**Data Availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## References

[1] National Alliance for Caregiving and AARP, Caregiving in the U.S. 2020 - AARP Research Report, 2020. https://www.caregiving.org/caregiving-in-the-us-2020/ (accessed June 9, 2020).

[2] P.P. Vitaliano, J. Zhang, J.M. Scanlan, Is caregiving hazardous to one's physical health? A meta-analysis, Psychol. Bull. 129 (6) (2003) 946–972.

[3] M. Pinquart, S. Sörensen, Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis, Psychol. Aging. 18 (2) (2003) 250–267.

[4] R. Schulz, S.R. Beach, Caregiving as a risk factor for mortality: the Caregiver Health Effects Study, JAMA. 282 (23) (1999) 2215–2219.

[5] M. Pinquart, S. Sörensen, Correlates of physical health of informal caregivers: a meta-analysis, J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 62 (2) (2007) P126–P137.

[6] S. Lee, G.A. Colditz, L.F. Berkman, I. Kawachi, Caregiving and risk of coronary heart disease in U.S. women: a prospective study, Am. J. Prev. Med. 24 (2) (2003) 113–119.

[7] B.D. Capistrant, J.R. Moon, L.F. Berkman, M.M. Glymour, Current and long-term spousal caregiving and onset of cardiovascular disease, J. Epidemiol. Community Health. 66 (10) (2012) 951–956.

[8] J.F. Buyck, J. Ankri, A. Dugravot, S. Bonnaud, H. Nabi, M. Kivimaki, A. Singh-Manoux, Informal caregiving and the risk for coronary heart disease: the Whitehall II study, J. Gerontol. A. Biol. Sci. Med. Sci. 68 (10) (2013) 1316–1323.

[9] A. Miyawaki, J. Tomio, Y. Kobayashi, H. Takahashi, H. Noguchi, N. Tamiya, Impact of long-hours family caregiving on non-fatal coronary heart disease risk in middle-aged people: results from a longitudinal nationwide survey in Japan, Geriatr. Gerontol. Int. 17 (11) (2017) 2109–2115.

[10] B.T. Mausbach, T.L. Patterson, Y.G. Rabinowitz, I. Grant, R. Schulz, Depression and distress

predict time to cardiovascular disease in dementia caregivers, Health Psychol. 26 (5) (2007) 539–544.

[11] Y. Kim, C.S. Carver, K.M. Shaffer, T. Gansler, R.S. Cannady, Cancer caregiving predicts physical impairments: roles of earlier caregiving stress and being a spousal caregiver, Cancer. 121 (2) (2015) 302–310.

[12] W.E. Haley, D.L. Roth, G. Howard, M.M. Safford, Caregiving strain and estimated risk for stroke and coronary heart disease among spouse caregivers differential effects by race and sex, Stroke. 41 (2) (2010) 331–336.

[13] P.J. Mills, S. Ancoli-Israel, R. von Kanel, B.T. Mausbach, K. Aschbacher, T.L. Patterson, M.G. Ziegler, J.E. Dimsdale, I. Grant, Effects of gender and dementia severity on Alzheimer's disease caregivers' sleep and biomarkers of coagulation and inflammation, Brain. Behav. Immun. 23 (5) (2009) 605–610.

[14] R. von Kanel, S. Ancoli-Israel, J.E. Dimsdale, P.J. Mills, B.T. Mausbach, M.G. Ziegler, T.L. Patterson, I. Grant, Sleep and biomarkers of atherosclerosis in elderly Alzheimer caregivers and controls, Gerontology. 56 (1) (2010) 41–50.

[15] R. von Kanel, J.E. Dimsdale, S. Ancoli-Israel, P.J. Mills, T.L. Patterson, C.L. McKibbin, C. Archuleta, I. Grant, Poor sleep is associated with higher plasma proinflammatory cytokine interleukin-6 and procoagulant marker fibrin D-dimer in older caregivers of people with Alzheimer's disease, J. Am. Geriatr. Soc. 54 (3) (2006) 431–437.

[16] P.H. Black, L.D. Garbutt, Stress, inflammation and cardiovascular disease, J. Psychosom. Res. 52 (1) (2002) 1–23.

[17] R. Wolk, A. Gami, A. Garciatouchard, V. Somers, Sleep and cardiovascular disease, Curr. Probl. Cardiol. 30 (12) (2005) 625–662.

[18] P. Ambrosino, R. Lupoli, A. Tortora, M. Cacciapuoti, G.A. Lupoli, P. Tarantino, A. Nasto, M.N.D. Di Minno, Cardiovascular risk markers in patients with primary aldosteronism: a systematic review and meta-analysis of literature studies, Int. J. Cardiol. 208 (2016) 46–55.

[19] K. Yao, T. Zhao, L. Zeng, J. Yang, Y. Liu, Q. He, X. Zou, Non-invasive markers of cardiovascular risk in patients with subclinical hypothyroidism: a systematic review and meta-analysis of 27 case control studies, Sci. Rep. 8 (1) (2018) 4579.

[20] J. Wang, X. Shi, C. Ma, H. Zheng, J. Xiao, H. Bian, Z. Ma, L. Gong, Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis, J. Hypertens. 35 (1) (2017) 10–17.

[21] E.A. Rosei, G. Chiarini, D. Rizzoni, How important is blood pressure variability?, Eur. Hear. J. Suppl. 22 (2020) E1–E6.

[22] G. Parati, C. Torlasco, M. Pengo, G. Bilo, J.E. Ochoa, Blood pressure variability: its relevance for cardiovascular homeostasis and cardiovascular diseases, Hypertens. Res. 43 (7) (2020) 609–620.

[23] S.L. Stevens, S. Wood, C. Koshiaris, K. Law, P. Glasziou, R.J. Stevens, R.J. McManus, Blood pressure variability and cardiovascular disease: systematic review and meta-analysis, BMJ. 354 (2016) i4098.

[24] P.F. Hsu, H.M. Cheng, C.H. Wu, S.H. Sung, S.Y. Chuang, E.G. Lakatta, F.C.P. Yin, P. Chou, C.H. Chen, High short-term blood pressure variability predicts long-term cardiovascular mortality in untreated hypertensives but not in normotensives, Am. J. Hypertens. 29 (7) (2016) 806–813.

[25] D. Sander, C. Kukla, J. Klingelhöfer, K. Winbeck, B. Conrad, Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis, Circulation. 102 (13) (2000) 1536–1541.

[26] A. Cremer, J. Doublet, R. Boulestreau, J. Gaudissard, C. Tzourio, P. Gosse, Short-term blood

pressure variability, arterial stiffness, and cardiovascular events: results from the Bordeaux cohort, J. Hypertens. 39 (5) (2021) 947–951.

[27] F. Saladini, C. Fania, L. Mos, O. Vriz, A. Mazzer, P. Spinella, G. Garavelli, A. Ermolao, M. Rattazzi, P. Palatini, Short-term but not long-term blood pressure variability is a predictor of adverse cardiovascular outcomes in young untreated hypertensives, Am. J. Hypertens. 33 (11) (2020) 1030–1037.

[28] S.H. Zarit, K.E. Reever, J. Bach-Peterson, Relatives of the impaired elderly: correlates of feelings of burden, Gerontologist. 20 (6) (1980) 649–655.

[29] R. Hébert, G. Bravo, M. Préville, Reliability, Validity and reference values of the Zarit Burden Interview for assessing informal caregivers of community-dwelling older persons with dementia, Can. J. Aging. 19 (4) (2000) 494–507.

[30] A.S. Schreiner, T. Morimoto, Y. Arai, S. Zarit, Assessing family caregiver's mental health using a statistically derived cut-off score for the Zarit Burden Interview, Aging Ment. Health. 10 (2) (2006) 107–111.

[31] S.Y. Al-Rawashdeh, T.A. Lennie, M.L. Chung, Psychometrics of the Zarit Burden Interview in caregivers of patients with heart failure, J. Cardiovasc. Nurs. 31 (6) (2016) E21–E28.

[32] B.K. Seng, N. Luo, W.Y. Ng, J. Lim, H.L. Chionh, J. Goh, P. Yap, Validity and reliability of the Zarit Burden Interview in assessing caregiving burden, Ann. Acad. Med. 39 (10) (2010) 758–763.

[33] K. Kroenke, R.L. Spitzer, J.B.W. Williams, The PHQ-9: validity of a brief depression severity measure, J. Gen. Intern. Med. 16 (9) (2001) 606–613.

[34] I.M. Cameron, J.R. Crawford, K. Lawton, I.C. Reid, Psychometric comparison of PHQ-9 and HADS for measuring depression severity in primary care, Br. J. Gen. Pract. 58 (546) (2008) 32–36.

[35] W. Wang, Q. Bian, Y. Zhao, X. Li, W. Wang, J. Du, G. Zhang, Q. Zhou, M. Zhao, Reliability and validity of the Chinese version of the Patient Health Questionnaire (PHQ-9) in the general population, Gen. Hosp. Psychiatry. 36 (5) (2014) 539–544.

[36] B. Gelaye, M.A. Williams, S. Lemma, N. Deyessa, Y. Bahretibeb, T. Shibre, D. Wondimagegn, A. Lemenhe, J.R. Fann, A. Vander Stoep, X.H. Andrew Zhou, Validity of the patient health questionnaire-9 for depression screening and diagnosis in East Africa, Psychiatry Res. 210 (2) (2013) 653–661.

[37] J. Mantua, N. Gravel, R.M.C. Spencer, Reliability of sleep measures from four personal health monitoring devices compared to research-based actigraphy and polysomnography, Sensors (Basel). 16 (5) (2016) 646.

[38] M. Marino, Y. Li, M.N. Rueschman, J.W. Winkelman, J.M. Ellenbogen, J.M. Solet, H. Dulin, L.F. Berkman, O.M. Buxton, Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography, Sleep. 36 (11) (2013) 1747–1755.

[39] M. Quante, E.R. Kaplan, M. Cailler, M. Rueschman, R. Wang, J. Weng, E.M. Taveras, S. Redline, Actigraphy-based sleep estimation in adolescents and adults: a comparison with polysomnography using two scoring algorithms, Nat. Sci. Sleep. 10 (2018) 13–20.

[40] J.A. Slater, T. Botsis, J. Walsh, S. King, L.M. Straker, P.R. Eastwood, Assessing sleep using hip and wrist actigraphy, Sleep Biol. Rhythms. 13 (2) (2015) 172–180.

[41] N. Cellini, M.P. Buman, E.A. McDevitt, A.A. Ricker, S.C. Mednick, Direct comparison of two actigraphy devices with polysomnographically recorded naps in healthy young adults, Chronobiol. Int. 30 (5) (2013) 691–698.

[42] R.J. Cole, D.F. Kripke, W. Gruen, D.J. Mullaney, J.C. Gillin, Automatic sleep/wake identification from wrist activity, Sleep. 15 (5) (1992) 461–469.

[43] P. Muntner, D. Shimbo, R.M. Carey, J.B. Charleston, T. Gaillard, S. Misra, M.G. Myers, G. Ogedegbe, J.E. Schwartz, R.R. Townsend, E.M. Urbina, A.J. Viera, W.B. White, J.T. Wright, Measurement of blood pressure in humans: a scientific statement from the American Heart Association, Hypertension. 73 (5) (2019) E35–E66.

[44] E. O'Brien, G. Parati, G. Stergiou, R. Asmar, L. Beilin, G. Bilo, D. Clement, A. de la Sierra, P. de Leeuw, E. Dolan, R. Fagard, J. Graves, G.A. Head, Y. Imai, K. Kario, E. Lurbe, J.-M. Mallion, G. Mancia, T. Mengden, M. Myers, G. Ogedegbe, T. Ohkubo, S. Omboni, P. Palatini, J. Redon, L.M. Ruilope, A. Shennan, J.A. Staessen, G. VanMontfrans, P. Verdecchia, B. Waeber, J. Wang, A. Zanchetti, Y. Zhang, European Society of Hypertension position paper on ambulatory blood pressure monitoring, J. Hypertens. 31 (9) (2013) 1731–1768.

[45] H. Schächinger, W. Langewitz, R.E. Schmieder, H. Rüddel, Comparison of parameters for assessing blood pressure and heart rate variability from non-invasive twenty-four-hour blood pressure monitoring, J. Hypertens. Suppl. 7 (3) (1989) S81-84.

[46] M. Yong, H.-C. Diener, M. Kaste, J. Mau, Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke, Stroke. 36 (12) (2005) 2619–2625.

[47] J. Östergren, H. Isaksson, Ambulatory blood pressure monitoring, Vasc. Med. Rev. 4 (2) (1993) 95–109.

[48] X. Ke, Y. Sun, R. Yang, J. Liang, S. Wu, C. Hu, X. Wang, Association of 24 h–systolic blood pressure variability and cardiovascular disease in patients with obstructive sleep apnea, BMC Cardiovasc. Disord. 17 (1) (2017) 287.

[49] X. Liu, G. Yan, L. Bullock, D.J. Barksdale, J.G. Logan, Sleep moderates the association between arterial stiffness and 24-hour blood pressure variability, Sleep Med. 83 (2021) 222–229.

[50] D. Shrivastava, S. Jung, M. Saadat, R. Sirohi, K. Crewson, How to interpret the results of a sleep

study, J. Community Hosp. Intern. Med. Perspect. 4 (5) (2014) 24983.

[51] K.S. Taylor, H. Murai, P.J. Millar, N. Haruki, D.S. Kimmerly, B.L. Morris, G. Tomlinson, T.D. Bradley, J.S. Floras, Arousal from sleep and sympathetic excitation during wakefulness, Hypertens. 68 (6) (2016) 1467–1474.

[52] L. Zanoli, M. Briet, J.P. Empana, P.G. Cunha, K.M. Maki-Petaja, A.D. Protogerou, A. Tedgui, R.M. Touyz, E.L. Schiffrin, B. Spronck, P. Bouchard, C. Vlachopoulos, R.M. Bruno, P. Boutouyrie, Vascular consequences of inflammation: a position statement from the ESH Working Group on Vascular Structure and Function and the ARTERY Society, J. Hypertens. 38 (9) (2020) 1682–1698.

[53] P. Gong, S.H. Yang, S. Li, S.H. Luo, R.X. Zeng, Y. Zhang, Y.L. Guo, C.G. Zhu, R.X. Xu, J.J. Li, Plasma d-dimer as a useful marker predicts severity of atherosclerotic lesion and short-term outcome in patients with coronary artery disease, Clin.Appl. Thromb. Hemost. 22 (7) (2016) 633–640.

[54] K.D. Monahan, F.A. Dinenno, D.R. Seals, C.M. Clevenger, C.A. Desouza, H. Tanaka, Age-associated changes in cardiovagal baroreflex sensitivity are related to central arterial compliance, Am. J. Physiol. Heart. Circ. Physiol. 281 (1) (2001) H284-289.

[55] I. Skrapari, N. Tentolouris, D. Perrea, C. Bakoyiannis, A. Papazafiropoulou, N. Katsilambros, Baroreflex sensitivity in obesity: relationship with cardiac autonomic nervous system activity, Obesity. 15 (7) (2007) 1685–1693.

[56] K. Eguchi, J. Ishikawa, S. Hoshide, T.G. Pickering, J.E. Schwartz, K. Shimada, K. Kario, Night time blood pressure variability is a strong predictor for cardiovascular events in patients with type 2 diabetes, Am. J. Hypertens. 22 (1) (2009) 46–51.

[57] A.E. Schutte, R. Schutte, H.W. Huisman, J.M. Van Rooyen, C.M.T. Fourie, N.T. Malan, L.

Malan, Blood pressure variability is significantly associated with ECG left ventricular mass in normotensive Africans: the SABPA Study, Hypertens. Res. 34 (10) (2011) 1127–1134.

[58] S. Cay, G. Cagirci, A.D. Demir, Y. Balbay, A.R. Erbay, S. Aydogdu, O. Maden, Ambulatory blood pressure variability is associated with restenosis after percutaneous coronary intervention in normotensive patients, Atherosclerosis. 219 (2) (2011) 951–957.

[59] C.J. McMullan, G.L. Bakris, R.A. Phillips, J.P. Forman, Association of BP variability with mortality among African Americans with CKD, Clin. J. Am. Soc. Nephrol. 8 (5) (2013) 731–738.

[60] P. Palatini, G. Reboldi, L.J. Beilin, E. Casiglia, K. Eguchi, Y. Imai, K. Kario, T. Ohkubo, S.D. Pierdomenico, J.E. Schwartz, L. Wing, P. Verdecchia, Added predictive value of night-time blood pressure variability for cardiovascular events and mortality: the Ambulatory Blood Pressure-International Study, Hypertens. 64 (3) (2014) 487–493.

[61] Á. García-García, L. García-Ortiz, J.I. Recio-Rodríguez, M.C. Patino-Alonso, C. Agudo-Conde, E. Rodriguez-Sanchez, M.A. Gómez-Marcos, Relationship of 24-h blood pressure variability with vascular structure and function in hypertensive patients, Blood Press. Monit. 18 (12) (2013) 101–106.

[62] V.M.A. Farah, L.F. Joaquim, I. Bernatova, M. Morris, Acute and chronic stress influence blood pressure variability in mice, Physiol. Behav. 83 (1) (2004) 135–142.

[63] D.K. Arnett, C.-C.S. Roger Blumenthal, C.-C.A. Michelle Albert, E.D. Michos, A.B. Buroker, M.D. Miedema, Z.D. Goldberger, D. Muñoz, E.J. Hahn, S.C. Smith, C.D. Himmelfarb, S.S. Virani, A. Khera, K.A. Williams, D. Lloyd-Jones, J. Yeboah, J. William McEvoy, B. Ziaeian, S.M. Al-Khatib, F.A. Mark Hlatky, F.K. Kim Birtcher, A. John Ikonomidis, J.E. Cigarroa, F.A. José Joglar, F. Anita Deswal, F. Laura Mauri, L.A. Fleisher, F.R. Mariann Piano, F. Federico Gentile, F. Barbara Riegel, D.N. Wijeysundera, 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. A report of the American College of Cardiology/American

Heart Association Task Force on clinical practice guidelines, Circulation. 140 (11) (2019) e596-e646.

**Table 1**

Characteristics of caregivers (N = 30).

| Characteristic | | n (%) | Mean (*SD*) |
|---|---|---|---|
| Age, years | | | 61.57 (11.63) |
| Sex | Female | 25 (83.3) | |
| | Male | 5 (16.7) | |
| Race/ethnicity | Non-Hispanic white | 27 (90.0) | |
| | Asian, Hispanic | 3 (10.0) | |
| Smoking | Never smoker | 21 (70.0) | |
| | Past/current smoker | 9 (30.0) | |
| Body mass index | | | 28.28 (5.43) |
| Sleep apnea | No | 24 (80.0) | |
| | Yes | 6 (20.0) | |
| Diabetes | No | 27 (90.0) | |
| | Yes | 3 (10.0) | |
| Antihypertensive medication | No | 23 (76.7) | |
| | Yes | 7 (23.3) | |
| Cholesterol medication | No | 22 (73.3) | |
| | Yes | 8 (26.7) | |
| Relationship with care recipient | | | |
| Spouse | | 18 (60.0) | |
| Adult child | | 4 (13.3) | |
| Parent(s) | | 3 (10.0) | |
| Multiple relationships | | 4 (13.3) | |
| Friend | | 1 (3.3) | |
| Care recipient's health condition | 1 condition | 9 (30.0) | |
| | 2 or more conditions | 21 (70.0) | |
| Caregiving hours per week | < 20 hours | 10 (33.3) | |
| | ≥ 20 hours | 20 (66.7) | |
| Caregiving duration | < 3 years | 13 (43.3) | |
| | ≥ 3 years | 17 (56.7) | |
| Caregiving stress | | | 37.30 (17.77) |
| Depressive symptoms | | | 6.00 (3.76) |

| | |
|---|---|
| Sleep duration, hours | 6.81 (0.89) |
| Sleep efficiency, % | 82.76 (6.61) |
| WASO, minutes | 80.92 (42.58) |
| Awakenings | 20.66 (7.43) |
| Office blood pressure, mmHg | |
| SBP | 121.87 (11.59) |
| DBP | 74.47 (9.09) |
| MAP | 90.27 (8.67) |
| BP-awake, mmHg | |
| SBP | 123.37 (9.87) |
| DBP | 73.19 (7.50) |
| BP-sleep, mmHg | |
| SBP | 109.96 (13.08) |
| DBP | 63.62 (7.74) |
| SV-24h, mmHg | |
| SBP | 13.07 (3.34) |
| DBP | 9.39 (2.18) |
| SV-awake, mmHg | |
| SBP | 13.67 (3.92) |
| DBP | 9.11 (2.46) |
| SV-sleep, mmHg | |
| SBP | 12.60 (4.94) |
| DBP | 10.31 (3.76) |

BP = blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; SV = successive variation; WASO = wake after sleep onset

**Table 2**

Bivariate correlations between predictors and blood pressure variability.

| | SBP | | | DBP | | |
|---|---|---|---|---|---|---|
| | SV-24h | SV-awake | SV-sleep | SV-24h | SV-awake | SV-sleep |
| Age | .165 | .158 | .123 | -.034 | -.127 | .059 |
| Sex | -.182 | -.264 | .124 | -.243 | -.135 | -.188 |
| Race | .123 | .141 | -.012 | .111 | .086 | .156 |
| Smoking | -.089 | -.198 | .194 | -.026 | -.061 | .050 |
| Body mass index | -.157 | -.100 | -.102 | .179 | .336 | -.091 |
| Sleep apnea | -.050 | -.210 | .330 | .219 | .023 | .214 |
| Diabetes | -.003 | .030 | -.031 | -.006 | .127 | -.118 |
| Hypertensive med | .166 | .331 | -.140 | -.194 | -.050 | -.219 |
| Cholesterol med | .224 | .287 | .055 | .285 | .359 | .076 |
| Mean arterial pressure | .335 | .408* | -.033 | .183 | .078 | .300 |
| Relationship | -.065 | -.139 | .029 | .043 | -.090 | .145 |
| Care-recipient health conditions | -.156 | -.192 | .042 | -.324 | -.286 | -.240 |
| Caregiving hours | .096 | .004 | .241 | -.185 | -.281 | .030 |
| Caregiving duration | .218 | .224 | .092 | .107 | -.034 | .145 |
| Caregiving stress | -.224 | -.294 | .074 | -.116 | -.115 | -.036 |
| Depression | -.314 | -.242 | -.141 | .196 | .263 | -.169 |
| Sleep efficiency | -.092 | -.232 | .074 | -.108 | -.368* | .286 |
| Wake after sleep onset | .128 | .303 | -.068 | .036 | .254 | -.311 |
| Awakenings | .335 | .426* | .120 | .250 | .422* | -.058 |

*$p < 0.05$

**Table 3**

Multiple linear regression including the number of awakenings for sleep quality.

| | SBP | | | DBP | | |
|---|---|---|---|---|---|---|
| | SV-24h | SV-awake | SV-sleep | SV-24h | SV-awake | SV-sleep |
| | *B* (95% CI) | | | *B* (95% CI) | | |
| Awakenings | 0.194 | 0.280 | 0.121 | 0.072 | 0.141 | -0.033 |
| | (0.036, 0.351)* | (0.116, 0.445)* | (-0.167, 0.408) | (-0.044, 0.188) | (0.015, 0.266) | (-0.247, 0.181) |
| Age | 0.078 | 0.099 | 0.149 | 0.032 | -0.003 | -0.008 |
| | (-0.022, 0.179) | (-0.006, 0.204) | (-0.108, 0.277) | (-0.043, 0.107) | (-0.083, 0.077) | (-0.151, 0.134) |
| MAP | 0.136 | 0.195 | 0.228 | 0.029 | 0.029 | 0.146 |
| | (0.006, 0.265)* | (0.059, 0.330)* | (-0.318, 0.224) | (-0.071, 0.128) | (-0.074, 0.133) | (-0.055, 0.134) |

*$p < 0.05$

DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; SV = successive variati

**Supplementary Table 1**

Bivariate correlations among predictors.

| | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | (11) | (12) | (13) | (14) | (15) | (16) | (17) | (18) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Age | | | | | | | | | | | | | | | | | | |
| 2 Sex | .007 | | | | | | | | | | | | | | | | | |
| 3 Race | -.014 | .211 | | | | | | | | | | | | | | | | |
| 4 Smoking | -.425* | .222 | .133 | | | | | | | | | | | | | | | |
| 5 BMI | -.046 | -.049 | -.205 | .145 | | | | | | | | | | | | | | |
| 6 Sleep apnea | .041 | .000 | -.107 | .155 | .208 | | | | | | | | | | | | | |
| 7 Diabetes | .032 | .149 | -.071 | .000 | .512** | .389* | | | | | | | | | | | | |
| 8 Hypertensive med | .283 | -.176 | -.118 | -.244 | .181 | -.079 | .079 | | | | | | | | | | | |
| 9 Cholesterol med | .214 | -.135 | -.129 | -.327 | .333 | .264 | .553* | .202 | | | | | | | | | | |
| 10 MAP | .029 | -.413* | .183 | -.318 | -.033 | -.182 | -.010 | .020 | .182 | | | | | | | | | |
| 11 Relationship with CR | -.055 | -.075 | .060 | .104 | -.106 | .549** | .180 | .004 | .017 | -.013 | | | | | | | | |
| 12 CR health conditions | -.146 | .293 | -.140 | .406* | -.080 | .145 | -.024 | .017 | -.263 | -.346 | .215 | | | | | | | |
| 13 Caregiving hours | -.101 | .253 | .242 | .351 | -.076 | .000 | .000 | -.111 | .107 | -.149 | -.118 | .154 | | | | | | |
| 14 Caregiving duration | .208 | -.211 | .014 | -.167 | -.128 | .101 | -.157 | -.154 | .071 | .248 | .004 | .015 | .238 | | | | | |
| 15 Caregiving stress | -.093 | .325 | .448* | .217 | .031 | .282 | .147 | -.095 | .046 | -.287 | .074 | .253 | .312 | .038 | | | | |
| 16 Depression | -.190 | .315 | .046 | .252 | .321 | .473** | .331 | -.085 | .408* | -.217 | .050 | .177 | .230 | .000 | .499** | | | |
| 17 Sleep efficiency | .047 | -.150 | -.007 | -.020 | -.090 | .017 | -.147 | -.287 | -.067 | -.079 | -.138 | -.094 | .178 | .089 | .131 | -.285 | | |
| 18 WASO | .045 | .113 | -.123 | .066 | .135 | -.025 | .117 | .382* | .087 | .033 | -.030 | .189 | -.089 | .001 | -.165 | .317 | -.926** | |
| 19 Awakenings | -.276 | -.096 | -.026 | .233 | .061 | -.097 | -.159 | .310 | -.056 | -.058 | -.079 | .105 | -.138 | -.133 | -.106 | .159 | -.719** | .750** |

*$p < .05$; **$p < .01$

BMI = body mass index, CR = care-recipient, MAP = mean arterial pressure, WASO = wake after sleep onset

**Supplementary Table 2**

Multiple linear regression including sleep efficiency for sleep quality.

| | SBP | | | DBP | | |
|---|---|---|---|---|---|---|
| | SV-24h | SV-awake | SV-sleep | SV-24h | SV-awake | SV-sleep |
| | *B* (95% CI) | | | *B* (95% CI) | | |
| Sleep efficiency | -0.037 (-0.227, 0.152) | -0.124 (-0.335, 0.086) | 0.052 (-0.268, 0.372) | -0.030 (-0.161, 0.100) | -0.134 (-0.273, 0.005) | 0.173 (-0.050, 0.395) |
| Age | 0.046 (-0.062, 0.153) | 0.053 (-0.066, 0.172) | 0.056 (-0.127, 0.239) | -0.006 (-0.080, 0.068) | -0.024 (-0.102, 0.055) | -0.003 (-0.130, 0.125) |
| MAP | 0.125 (-0.019, 0.269) | 0.175 (0.015, 0.335)* | -0.036 (-0.310, 0.239) | 0.045 (-0.055, 0.144) | 0.015 (-0.091, 0.121) | 0.152 (-0.039, 0.343) |

DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure; SV = successive variation

# Chapter 6: Conclusions

Family caregivers play a pivotal role in the current healthcare system. Although many caregivers find caregiving rewarding and perceive it as an opportunity for personal growth, ongoing demands can be a psychological and physical burden. High stress related to providing care has been associated with deleterious effects on caregivers' health. Caregiving burden and alterations in health behavior resulting from caregivers' duties and limited time for selfcare are known to have implications for cardiovascular disease (CVD) risk among caregivers. To understand the links of the psychological and behavioral factors to cardiovascular health among caregivers, this dissertation presents the evidence of CVD risk in caregivers through a systematic review of the literature and the findings from a cross-sectional study using a subclinical marker to assess CVD risk in relation to psychological symptoms and sleep quality.

## Summary of Findings

The first manuscript of this dissertation highlighted caregivers' vulnerability to CVD development, providing evidence of higher CVD incidence rates and CVD risk as represented by various biomarkers and measures. The reviewed studies reported that caregivers experienced up to twice the incidence of CVD compared to non-caregivers, and the detrimental effects of caregiving on CVD incidence were more pronounced in long-term caregivers, caregivers of patients with high mortality rates, and those with poor mental and physical health. Caregivers exhibited more frequent CVD risk factors, e.g., higher inflammatory biomarker levels, higher risk of having carotid plaque, more blunted heart rate variability. Furthermore, hypertension and metabolic syndrome were more prevalent in caregivers, and global CVD risk scores that are calculated using the presence of various risk factors were significantly higher in caregivers than non-caregivers. The caregivers' increased CVD risk was associated with longer caregiving hours and duration, poorer care-recipient's health status, poor sleep quality, short sleep duration, as well as high psychological symptoms.

The dissertation study focused on the relationships among psychological symptoms, sleep quality, and CVD risk in caregivers of patients with chronic illness. The study sample consisted of 34 caregivers

who provided in-home care for their loved ones. The study assessed psychological and behavioral factors as independent variables: caregiving stress, depression, and anxiety were indicators of psychological factors; objective sleep quality (sleep efficiency, wake after sleep onset, number of awakenings) was the indicator of behavioral factors. The outcome variable was short-term blood pressure variability (BPV) indicating CVD risk. Psychological symptoms data were collected using questionnaires, sleep quality data using actigraphy for 7 days, and short-term BPV data using 24-hour ambulatory blood pressure monitoring.

In the second manuscript, characteristics of caregivers' sleep quality transitions over time and distinct impacts of psychological symptoms by their levels on the dynamics and patterns of sleep quality states were revealed through Markov chain modeling. Caregivers tended to have consistent sleep efficiency states on a night-to-night basis, which implies a drop in sleep efficiency does not recover to a normal state in a short time but takes at least 4-5 days. Psychological symptoms seemed to affect the sleep patterns in that probabilities of transitioning to a normal sleep efficiency state were lower in the high depression and anxiety groups compared to the low symptom groups. The long-term probability of maintaining optimal sleep efficiency was significantly lower for caregivers with elevated levels of depression and anxiety compared to their counterparts with low symptoms. These findings suggest that caregivers' psychological symptoms may adversely affect sleep quality patterns over time and highlight the need for caregiver support to manage psychological burdens in an effort to prevent sustained suboptimal sleep quality.

The third manuscript examines the associations of psychological symptoms and sleep quality with CVD risk. The sample contained 30 caregivers who had complete sets of physiological data (objective sleep and ambulatory blood pressure). The results demonstrated that higher sleep efficiency was significantly correlated with lower diastolic BPV while awake; and a greater number of awakenings during sleep was significantly correlated with higher systolic/diastolic BPV while awake. Caregiving stress and depression were not correlated with BPV. When potential confounding factors, including age and mean arterial pressure, were taken into account, the number of awakenings was an independent

predictor of increased systolic BPV over 24 hours and while awake. This finding suggests that caregivers' disrupted sleep, represented by frequent awakenings, may well play a role in increased CVD risk. Poor sleep quality may lead to augmented sympathetic nervous system and impaired arterial compliance that are implicated in hemodynamic changes. The finding underscores the importance of maintaining optimal sleep quality in CVD prevention strategies for caregivers. This study should be replicated in larger clinical studies to reinforce the relationships observed.

**Nursing Implications**

There are several nursing implications of this study for healthcare providers and researchers. In terms of clinical implications, healthcare providers should pay more attention to assessing caregivers' sleep status and cardiovascular health. In primary healthcare settings, it is important to identify individuals who are providing informal care to their loved ones and to assess the caregiving duties that may take a toll on their health. For caregivers, assessment of psychological symptoms (i.e., depression, anxiety), sleep problems, and barriers to good quality sleep should be incorporated into routine clinical check-ups, followed by referring to resources as appropriate. Caregiver assistance with sleep problems will vary depending upon cause, such as psychological burden, insomnia, nighttime caregiving, or care recipient behavior problems that commonly manifest at night. Cognitive-behavioral therapy and mindfulness training have shown potential for positive effects on alleviating insomnia and psychological symptoms (Carter et al., 2009; Paller et al., 2015). For causes more directly linked to caregiving duties, tangible and practical resources and support services that assist caregivers with caregiving tasks and managing their care recipient's health conditions should be provided (McCurry et al., 2005). Nurses are well-positioned to recognize the needs of caregivers, provide them with education, and coordinate care and support. It is critical that nurses be aware of psychological symptoms and poor sleep quality that are likely to impact caregivers' cardiovascular health.

Regarding research implications, this study calls for a more comprehensive understanding of factors that influence caregivers' health behavior and self-care practices, such as stress management and sleep hygiene practice. Given that caregiving is a complex phenomenon related to individual,

interpersonal, social, and environmental factors, further efforts in understanding the predisposing, precipitating, and perpetuating barriers and facilitators to maintaining caregivers' cardiovascular health are warranted. Knowledge of modifiable factors can inform future interventions aimed at improving cardiovascular health for caregivers. Interventions focused on sleep disturbance and psychological symptoms should be tested in a larger caregiver sample. Whether positive effects on sleep or psychological symptoms can attenuate cardiovascular risk also should be investigated. In addition, this study implies that utilizing subclinical CVD markers may broaden the body of knowledge on potential mechanisms in which caregiver cardiovascular health may deteriorate. Surrogate markers, such as BPV, may help identify subgroups of caregivers who are at risk of CVD but otherwise present as healthy. These individuals may benefit from implementing strategies for mitigating detrimental consequences of caregiving on cardiovascular health. For reliable evidence on the utility of subclinical markers for primary CVD prevention in caregivers, rigorous studies that assess longitudinal CVD risk using these markers in a large caregiver sample are needed. The evidence can help raise awareness of caregivers' vulnerability to a decline in cardiovascular health and call for actions to set the stage for policies to care for caregivers.

**Strengths and Limitations**

This study has a novelty in two aspects. To our knowledge, this was one of the first attempts to examine cardiovascular health of caregivers using short-term BPV. Despite the prognostic significance of the subclinical marker that has been proven in various populations, it has not been utilized for assessing CVD risk in the population of caregivers. Especially, this study sought to examine BPV in relation to psychological symptoms and sleep quality that are documented as the most common negative influences on caregiver health and wellbeing. In addition, this study was the first to apply Markov chain modeling to objectively measured sleep quality data for examining caregivers' sleep patterns over time. Considering that most evidence of caregiver sleep status are based on self-reported sleep quality and average values of objective sleep parameters, this study provided a new insight into temporal characteristics of caregivers' sleep patterns and their variations affected by psychological symptoms.

Despite these merits, there are several limitations that should be considered in interpreting the

results. First, this study had a small convenience sample with white-dominant participants. The study findings should be confirmed in a larger sample with racial/ethnic diversity. A larger sample size would also allow potential confounding factors (e.g., comorbidity, health behavior, or caregiving characteristics) of CVD risk to be considered. Second, the nature of cross-sectional design precludes inferring causal relationships among psychological, behavioral factors and cardiovascular risk. Prospective, longitudinal studies are warranted.

In conclusion, this dissertation study examined cardiovascular risk on caregivers in relation to psychological symptoms and sleep quality. Understanding modifiable psychobehavioral factors is a critical step to develop interventions promoting cardiovascular health of caregivers. Knowledge of the associations among the factors and their impacts on subclinical cardiovascular conditions can increase awareness of the importance of providing supports directed towards primary CVD prevention strategies. More attention should be paid by healthcare providers and researchers toward psychological burden and sleep disturbance that caregivers commonly experience, as well as self-care practices that can alleviate the detrimental effects of caregiving on cardiovascular health in caregivers. Compromised caregiver health may be linked to reduced quality of caregiving to care-recipients. In addition, compromised caregiver health can be a costly burden on the healthcare system, especially if caregivers are no longer able to provide home care, resulting in institutionalization. Thus, attending to caregivers' health is critical to improving outcomes for the care recipients and caregivers, and for preserving the healthcare system.

## References

Carter, P. A., Mikan, S. Q., & Simpson, C. (2009). A feasibility study of a two-session home-based cognitive behavioral therapy-insomnia intervention for bereaved family caregivers. *Palliative & Supportive Care*, *7*(2), 197–206. https://doi.org/10.1017/S147895150900025X

McCurry, S. M., Gibbons, L. E., Logsdon, R. G., Vitiello, M. V, & Teri, L. (2005). Nighttime insomnia treatment and education for Alzheimer's disease: A randomized, controlled trial. *Journal of the American Geriatrics Society*, *53*(5), 793–802. https://doi.org/10.1111/j.1532-5415.2005.53252.x

Paller, K. A., Creery, J. D., Florczak, S. M., Weintraub, S., Mesulam, M.-M., Reber, P. J., Kiragu, J., Rooks, J., Safron, A., Morhardt, D., O'Hara, M., Gigler, K. L., Molony, J. M., & Maslar, M. (2015). Benefits of mindfulness training for patients with progressive cognitive decline and their caregivers. *American Journal of Alzheimer's Disease and Other Dementias*, *30*(3), 257–267. https://doi.org/10.1177/1533317514545377

# Appendices

Appendix 1. Questionnaire Packet

## Zarit Burden Interview (ZBI)

The following in a list of statements that reflect how people sometimes feel when taking care of another person. After each statement, please indicate **how often you feel that way**: *never, rarely, sometimes, quite frequently, or nearly always*. There are no right or wrong answers.

| | Never | Rarely | Sometimes | Quite frequently | Nearly always |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| 1. Do you feel that your relative asks for more help than he/she needs? | | | | | |
| 2. Do you feel that because of the time you spend with your relative that you don't have enough time for yourself? | | | | | |
| 3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work? | | | | | |
| 4. Do you feel embarrassed over your relative's behavior? | | | | | |
| 5. Do you feel angry when you are around your relative? | | | | | |
| 6. Do you feel that your relative currently affects your relationships with other family members or friends in a negative way? | | | | | |
| 7. Are you afraid what the future holds for your relative? | | | | | |
| 8. Do you feel your relative is dependent on you? | | | | | |
| 9. Do you feel strained when you are around your relative? | | | | | |
| 10. Do you feel your health has suffered because of your involvement with your relative? | | | | | |

| | Never | Rarely | Sometimes | Quite frequently | Nearly always |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| 11. Do you feel that you don't have as much privacy as you would like because of your relative? | | | | | |
| 12. Do you feel that your social life has suffered because you are caring for your relative? | | | | | |
| 13. Do you feel uncomfortable about having friends over because of your relative? | | | | | |
| 14. Do you feel that your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on? | | | | | |
| 15. Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses? | | | | | |
| 16. Do you feel that you will be unable to take care of your relative much longer? | | | | | |
| 17. Do you feel you have lost control of your life since your relative's illness? | | | | | |
| 18. Do you wish you could leave the care of your relative to someone else? | | | | | |
| 19. Do you feel uncertain about what to do about your relative? | | | | | |
| 20. Do you feel you should be doing more for your relative? | | | | | |
| 21. Do you feel you could do a better job in caring for your relative? | | | | | |
| | Not at all | A little | Moderately | Quite a bit | Extremely |
| 22. Overall, how burdened do you feel in caring for your relative? | | | | | |

## Patient Health Questionnaire-9

| **Over the last 2 weeks, how often have you been bothered by any of the following problems?** *(Use "✔" to indicate your answer)* | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
|---|---|---|---|---|
| **1.** Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| **2.** Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| **3.** Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| **4.** Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| **5.** Poor appetite or overeating | 0 | 1 | 2 | 3 |
| **6.** Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| **7.** Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| **8.** Moving or speaking so slowly that other people could have noticed? Or so fidgety or restless that you have been moving around a lot more than usual. | 0 | 1 | 2 | 3 |
| **9.** Thoughts that you would be better off dead or of hurting yourself in some way. | 0 | 1 | 2 | 3 |
| **FOR OFFICE CODING** *0* | | | **+ _____ + _____ + _____** | |
| | | | **=Total Score: _____** | |

**If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made it for you to do your work, take care of things at home, or get along with other people?**

| **Not difficult at all** | **Somewhat difficult** | **Very difficult** | **Extremely difficult** |
|---|---|---|---|
| … | … | … | … |

## General Anxiety Disorder (GAD) – 7

**How often have you been bothered by the following over the past 2 weeks?**

| | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| Feeling nervous, anxious, or on edge | | | | |
| Not being able to stop or control worrying | | | | |
| Worrying too much about different things | | | | |
| Trouble relaxing | | | | |
| Being so restless that it's hard sit still | | | | |
| Becoming easily annoyed or irritable | | | | |
| Feeling afraid as if something awful might happen | | | | |

**Caregiver Information Form (CIF)**

1. What is your age (in years)? _____

2. What is your sex?

□ Male □ Female □ Other (Please specify: _____) □ Prefer not to say

3. How do you identify yourself in race/ethnicity?

□ Hispanic

□ Non-Hispanic White

□ Non-Hispanic Black or African American

□ Non-Hispanic American Indian or Alaska Native

□ Non-Hispanic Asian

□ Non-Hispanic Native Hawaiian or other Pacific Islander

□ Other (Please specify: _____ )

4. Are you smoking currently?

□ Current-smoker

□ Past-smoker

□ Never-smoker

5. Have you been diagnosed with any sleep disorder?

□ Yes **(Go to 5-1 below)** □ No **(Go to 6 below)**

5-1. Is the known sleep disorder obstructive sleep apnea?

□ Yes **(Go to 5-2 below)** □ No

5-2. If you are diagnosed with obstructive sleep apnea, are you currently using CPAP?

□ Yes

□ No

6. Do you currently take medication(s) for high blood pressure? □ Yes (Name: _____) □ No

7. Do you currently take medication(s) for high cholesterol? □ Yes □ No

8. Do you currently take medication(s) for diabetes? □ Yes □ No

9. In general, would you say your health is…

□ Excellent

□ Very good

□ Good

□ Fair

□ Poor

**Think about the individual for whom you are currently providing the most care.**

10. Whom are your currently caring for?

□ an adult child

□ a spouse/partner

□ a parent/parents

□ a friend or other non-relative

□ another family member

□ Other (Please specify: _____ )

11. Please check all conditions for which you have provided care for this person. (Check all that apply)

□ Cancer (lymphoma, leukemia, solid tumor)

□ Cardiovascular disease (e.g., coronary heart disease, congestive heart failure, etc.)

□ Pulmonary disease (e.g., COPD, asthma, etc.)

□ Liver disease

□ Kidney disease

□ Cerebrovascular disease (e.g., stroke)

□ Dementia or Alzheimer's

□ Rheumatic or connective tissue disease

□ Parkinson disease

□ HIV / AIDS

□ Neurological issues

□ Orthopedic/musculoskeletal issues

□ Aging/aging-related health issues

□ Mental health/behavioral issues

□ Other (Please specify:_____)

12. Thinking of all of the kinds of help you provide for this person, about how many hours do you spend in an average week providing care?

_____ hours/week

13. About how long have you been providing care for this person?

_____ months

***Thank you for participating in this research project!***

Appendix 2. Sleep Diary

**SLEEP DIARY**

ID#: _____

Date: _____

(MM/DD/YYYY)

**Instruction for recording**

- Please do NOT remove the device for full a day (24 hours). If you need to remove it, please record the time you take it off and the time you put it back on (for example, when taking a shower or bath).
- In the morning, please answer the questions in the top section about your sleep the night before.
- In the evening, please answer the questions in the bottom section about your day.

Wear Time: _____ ~ _____
(MM/DD/YYYY) (HH:MM) (MM/DD/YYYY) (HH:MM)

**Complete in the Evening (DAY 1)**

| | | |
|---|---|---|
| Did you take any naps or doze off during the day or evening today? | Yes / No | |
| • If *yes*, how much time did you sleep during the day or evening today? | _____ minutes / hours | |
| Did you take off the sleep watch today? | Yes / No | |
| • If *yes*, please record what time you took it off and put it back on. | ( : ) ~ ( : ) | ( : ) ~ ( : ) |
| | ( : ) ~ ( : ) | ( : ) ~ ( : ) |

**Complete in the Morning (DAY 2)**

| | |
|---|---|
| What time did you go to bed last night? | _____PM/AM |
| Did you wake up during the night? | Yes / No |
| • If *yes*, how many times? | |
| • If *yes*, how much time total were you awake? | |
| What time did you get up today? | _____ AM |
| About how many hours did you sleep last night? | _____hours |

**Complete in the Evening (DAY 2)**

| | | |
|---|---|---|
| Did you take any naps or doze off during the day or evening today? | Yes / No | |
| • If *yes*, how much time did you sleep during the day or evening today? | _____ minutes / hours | |
| Did you take off the sleep watch today? | Yes / No | |
| • If *yes*, please record what time you took it off and put it back on. | ( : ) ~ ( : ) | ( : ) ~ ( : ) |
| | ( : ) ~ ( : ) | ( : ) ~ ( : ) |

**Complete in the Morning (DAY 3)**

| | |
|---|---|
| What time did you go to bed last night? | _____PM/AM |
| Did you wake up during the night? | Yes / No |
| • If *yes*, how many times? | |
| • If *yes*, how much time total were you awake? | |
| What time did you get up today? | _____ AM |
| About how many hours did you sleep last night? | _____hours |

**Complete in the Evening (DAY 3)**

| | | |
|---|---|---|
| Did you take any naps or doze off during the day or evening today? | Yes / No | |
| • If *yes*, how much time did you sleep during the day or evening today? | _____ minutes / hours | |
| Did you take off the sleep watch today? | Yes / No | |
| • If *yes*, please record what time you took it off and put it back on. | ( : ) ~ ( : ) | ( : ) ~ ( : ) |
| | ( : ) ~ ( : ) | ( : ) ~ ( : ) |

**Complete in the Morning (DAY 4)**

| | |
|---|---|
| What time did you go to bed last night? | _____PM/AM |
| Did you wake up during the night? | Yes / No |
| • If *yes*, how many times? | |
| • If *yes*, how much time total were you awake? | |
| What time did you get up today? | _____ AM |
| About how many hours did you sleep last night? | _____hours |

**Complete in the Evening (DAY 4)**

| | | |
|---|---|---|
| Did you take any naps or doze off during the day or evening today? | Yes / No | |
| • If *yes*, how much time did you sleep during the day or evening today? | _____<br>minutes / hours | |
| Did you take off the sleep watch today? | Yes / No | |
| • If *yes*, please record what time you took it off and put it back on. | ( : )<br>~ ( : ) | ( : )<br>~ ( : ) |
| | ( : )<br>~ ( : ) | ( : )<br>~ ( : ) |

**Complete in the Morning (DAY 5)**

| | |
|---|---|
| What time did you go to bed last night? | _____PM/AM |
| Did you wake up during the night? | Yes / No |
| • If *yes*, how many times? | |
| • If *yes*, how much time total were you awake? | |
| What time did you get up today? | _____ AM |
| About how many hours did you sleep last night? | _____hours |

**Complete in the Evening (DAY 5)**

| | | |
|---|---|---|
| Did you take any naps or doze off during the day or evening today? | Yes / No | |
| • If *yes*, how much time did you sleep during the day or evening today? | _____ minutes / hours | |
| Did you take off the sleep watch today? | Yes / No | |
| • If *yes*, please record what time you took it off and put it back on. | ( : ) ~ ( : ) | ( : ) ~ ( : ) |
| | ( : ) ~ ( : ) | ( : ) ~ ( : ) |

**Complete in the Morning (DAY 6)**

| | |
|---|---|
| What time did you go to bed last night? | _____PM/AM |
| Did you wake up during the night? | Yes / No |
| • If *yes*, how many times? | |
| • If *yes*, how much time total were you awake? | |
| What time did you get up today? | _____ AM |
| About how many hours did you sleep last night? | _____hours |

**Complete in the Evening (DAY 6)**

| | | |
|---|---|---|
| Did you take any naps or doze off during the day or evening today? | Yes / No | |
| • If *yes*, how much time did you sleep during the day or evening today? | _____ minutes / hours | |
| Did you take off the sleep watch today? | Yes / No | |
| • If *yes*, please record what time you took it off and put it back on. | ( : ) ~ ( : ) | ( : ) ~ ( : ) |
| | ( : ) ~ ( : ) | ( : ) ~ ( : ) |

**Complete in the Morning (DAY 7)**

| | |
|---|---|
| What time did you go to bed last night? | _____PM/AM |
| Did you wake up during the night? | Yes / No |
| • If *yes*, how many times? | |
| • If *yes*, how much time total were you awake? | |
| What time did you get up today? | _____ AM |
| About how many hours did you sleep last night? | _____hours |

**Complete in the Evening (DAY 7)**

| | | |
|---|---|---|
| Did you take any naps or doze off during the day or evening today? | Yes / No | |
| • If *yes*, how much time did you sleep during the day or evening today? | _____<br>minutes / hours | |
| Did you take off the sleep watch today? | Yes / No | |
| • If *yes*, please record what time you took it off and put it back on. | ( : )<br>~ ( : ) | ( : )<br>~ ( : ) |
| | ( : )<br>~ ( : ) | ( : )<br>~ ( : ) |

**Complete in the Morning (DAY 8)**

| | |
|---|---|
| What time did you go to bed last night? | _____PM/AM |
| Did you wake up during the night? | Yes / No |
| • If *yes*, how many times? | |
| • If *yes*, how much time total were you awake? | |
| What time did you get up today? | _____ AM |
| About how many hours did you sleep last night? | _____hours |

***Thank you for participating in the study!***