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24-Hours of Heart Health: An Analysis of Sleep Duration and Cardiovascular Disease in the OPACH Cohort

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24-Hours of Heart Health: An Analysis of Sleep Duration and Cardiovascular Disease in the  
OPACH Cohort

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

in

Public Health (Health Behavior)

by

Kelsie M. Full

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University of California San Diego

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San Diego State University

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Professor Linda Gallo

2018

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The Dissertation of Kelsie M. Full is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California San Diego

San Diego State University

2018

## **DEDICATION**

To my tribe: family and chosen family.

Thank you for always *knowing* me.

## **EPIGRAPH**

Sleep can completely change your entire outlook on life. One good night's sleep can help you realize that you shouldn't break up with someone, or you are being too hard on your friend, or you actually will win the race or the game or get the job.

Sleep helps you win at life.

– Amy Poehler, comedian, on sleep

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Beyond my immediate family, my closest girlfriends have been incredible. I know living in San Diego helps a bit, but one of you girls jump on a plane each and every time I say I’m lonely. Staying close over a distance, and staying connected, is incredibly difficult. Avery, Nicole, Anita, Kitty, Claire, Marvio, Kori, Meg and Rachel. I realized when I moved out here and had to make new friends, how special you all are to me. How rare it is to have so many close friends in my life. Thank you for always answering the phone, even when I forget what time zone you are in. Thank you for making sure I’m alive when I disappear. And thank you for always, always making me feel like you are there, even when “there” is relative.

When I moved to San Diego five years ago, I knew three people. I knew nothing about this city and had no idea what to expect. I also had no idea that kind strangers would become friends and then become family. From baristas to soccer moms to frolleagues, I found my chosen family in unexpected places. I could not have made it through the day to day, and through piles of laundry, without you. Brittney, Eileen, Michelle, Lindsay and Katie. Sarah and Kev. Mas, Katrina and Bree. Jamie. Courtney and Eric. And all of the soccer families. I am so thankful you came into my life.

Last, but certainly not least, I would like to thank Dr. Kerr. When we had coffee in 2015, I had very little expectations but very high hopes that I would have the opportunity to work with you. Thank you for taking me under your wing. Saying thank you is not enough. Not even close. You have been the definition of constant. You have helped me build my confidence in myself in ways I never expected. Of all of the lessons I learned from you, I think most important of all, “I know myself”. I know what my strengths are. I know it's more important to be the best version of myself instead of a mediocre version of someone else. Thank you for teaching me, for mentoring me, and for always being there for me.

Thank you to my team of sleep coders. Thank you for being committed to our work and for showing up and caring as much as you have. Dana, Divya, Krezia, you girls are awesome. And a very special thank you to Drs. Malhotra, LaCroix, Gallo, and Arredondo for being so responsive and support throughout this process. It has been incredibly enjoyable and I am so thankful for all that I have learned.

When they say it takes a village, I do not think they were referring to finishing a PhD. But, it's true. I am so fortunate for the humans in my village. Thank you. Thank you. My cup runneth over.

Chapter 1 is currently being prepared for submission for the publication of the material. Co-authors include Drs. Jacqueline Kerr, Atul Malhotra, Linda Gallo, John Bellettiere, Elva Arredondo, Katie L. Stone, Oleg Zaslavsky, Cora E. Lewis, Xiaochen Lin, and Andrea Z. LaCroix. The dissertation author was the primary investigator and author of this material.

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### EDUCATION

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- 2012 Master of Public Health, Community Health Sciences. University of Illinois at Chicago, School of Public Health
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Department of Family Medicine & Public Health | San Diego, CA | University of California San Diego

*Data Manager*

Responsible for the management of data collected from an NCI funded R01 and a NHLBI funded R01 projects. Leads processing, cleaning, and analysis of participant survey data, biomarker exposure data, 24 hour accelerometry data, and GPS device data.

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PEP4PA - Peer Empowerment Program for Physical Activity in Low Income & Minority Seniors. Two year cluster randomized, controlled field trial of ethnically diverse, older adults (50+ years old) in 12 low income senior centers in San Diego County. Study aims to investigate the efficacy of PEP4PA to reduce disparities in PA by increasing the percentage of participants achieving 150 minutes of PA per week and to improve physical functioning & fitness, blood pressure, depressive symptoms and quality of life at 6, 12 & 24 months.
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August 2013 – March 2015

Institute for Behavioral and Community Health | San Diego, CA | San Diego State University

*Graduate Research Assistant*

Assisted in both intervention and evaluation components of the CDC-funded Childhood Obesity Research Demonstration study known as *Our Choice/Nuestra Opcion*.

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SDSU Graduate School of Public Health | San Diego, CA | San Diego State University  
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Directed participant enrollment, implementation evaluation activities, and survey data collection for a national multi-site youth mentoring randomized trial evaluation of Big Brothers Big Sisters of America programs. Responsible for the management of 30 databases including the tracking of study participants and all intervention site staff.

- OJJDP (Dubois) N=900  
Agency-Level Randomized Trial of the Effectiveness of Youth-Centered Match Support as a Delinquency Prevention Strategy in Community-Based Mentoring.  
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- Full, K.M.**, Schmied, E., Parada, H., Cherrington, A., Horton, L., Ayala, G.X. (2017). The relationship between sleep duration and diabetes control among Hispanic adults with type 2 diabetes. *Diabetes Educator*, 43 (5), 519 -529.
- Rich, P., Aarons, G., Cardenas, V., Crist, K., Bolling, K., Lewars, B., Castro-Sweet, C., Natarajan, L., Shi, Y., **Full, K.M.**, Johnson, E., Takemoto, M., & Kerr, J. (2017). Implementation-Effectiveness Trial of an Ecological Intervention for Physical Activity in Ethnically Diverse Low Income Senior Centers. *BMC Public Health*, 18(1), 29.
- Murray, K, Godbole, S, Natarajan, L, **Full, K.M.**, Hipp, A, Glanz, K, Mitchell, J, Laden, F, James, P, Quante, M, & Kerr, J. (2017). The Relations between Sleep, Time of Physical Activity, and Time Outdoors Among Older Adult Women. *PLOS ONE*. 12(9): e0182013.
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- Din, H., Cervantes, G., **Full, K.M.**, Moody, J., Ibarra, L., Binggeli-Vallarta, A., Ayala, G. X. Sleeping for health: an assessment of healthy sleep promotion in elementary schools. Poster session at the International Society for Behavioral Nutrition and Physical Activity Annual Conference, San Diego, CA, May 2014.
- Full, K.M.**, Binggeli-Vallarta, A., Cervantes, G., Moody, J., Din, H., Ayala, G. X. Physical Activity & Sedentary Behavior in the Childcare Setting: Identifying System, Environment, and Policy Factors for Modification. Poster session at the SDSU Student Research Symposium, San Diego, CA, March 2014.
- Slater, S., **Full, K.M.**, Fitzgibbon, M. Test-retest Reliability and Validity Results of the Youth Physical Activity Supports Questionnaire. Poster session at the International Society for Behavioral Nutrition and Physical Activity Annual Conference, Austin, TX, May 2012.

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## **MERIT AWARDS**

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## **SERVICE**

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San Diego State University & University of California – San Diego  
Joint Doctoral Program in Public Health

*Health Behavior Track Student Representative*

Nominated by peers to serve as a representative for students in the health behavior track in the JDP Doctoral Program steering committee meetings to support and foster good communication between the faculty and students.

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Chicago Adventure Therapy | Chicago, IL

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Facilitated and led youth development and outdoor education programs created for at-risk youth.

## ABSTRACT OF THE DISSERTATION

24-Hours of Heart Health: An Analysis of Sleep Duration and Cardiovascular Disease in the  
OPACH Cohort

by

Kelsie M. Full

Doctor of Philosophy in Public Health (Health Behavior)

University of California San Diego, 2018  
San Diego State University, 2018

Professor Jacqueline Kerr, Chair

**Background:** Cardiovascular Disease (CVD) is the most prevalent chronic disease in the aging population. Older women are at greatest risk for CVD, higher than their male counterparts. Disparities in the incidence and prevalence of CVD and CVD risk factors in older women, suggest that current prevention strategies are not effective for these populations. Research shows that post-menopausal women experience difficulty adapting to age-related changes in sleep. Considering 1/3 of the day is spent sleeping, sleep duration is a potential modifiable CVD lifestyle risk factor worthy of greater exploration. Aging research to date has included a focus on the cardiometabolic associations of sleep duration, including large-scale epidemiological studies

and meta-analyses concluding that inadequate sleep duration and poor sleep quality are associated with increased development, progression, and severity of CVD and CVD comorbidities. Research, however, has mostly employed self-reported sleep measures, focused on Caucasian populations and has not considered sleep as part of the 24 hour day. There is a need for research to examine the relationship between sleep duration and CVD risk in an older population of women, and to determine if insufficient sleep duration, short or long, is a CVD risk factor worthy of further examination.

**Methods:** This dissertation leverages data from the unique “Objective Physical Activity and Cardiovascular Health” (OPACH) study among 6489 women, ages 63-99, recruited from a Women’s Health Initiative cohort. Women wore ActiGraph GT3X+ accelerometers on the hip for 24 hours per day and completed a daily sleep log over a 7-day period. In addition to accelerometer-measured 24-hour activity data, the OPACH study includes measures of physical functioning, lifestyle questionnaires, and clinical biomarkers. Participants were contacted yearly to provide updated medical history including self-report of CVD events with follow-up up to 5 years. Sleep data were scored according to a standard protocol using sleep logs. Chapter 1 assessed if sleep duration, measured with accelerometers, is associated with numerous cardiometabolic markers, including measures of insulin resistance, inflammation and body composition in older women. Chapter 2 was an examination of the relationship between sleep duration and the Reynolds Risk Score, a clinically relevant composite CVD risk score. In Chapter 3, the relationship between cardiovascular events over 3-5 years of follow-up and self-reported sleep duration and accelerometer-measured sleep duration was examined.

**Results:** Chapter 1 found significant associations between sleep duration and markers of cardiometabolic health. Several of these relationships suggested the relationship was u-shaped,

with short and long sleep associated with higher cardiometabolic values. Chapter 2 further explored this relationship and demonstrated that sleep duration is non-linearly associated with 10-year estimated CVD risk among older women. In Chapter 3, there was no significant increase in CVD risk for short or long sleep durations over the 5-year period, measured by self-report or accelerometer.

**Discussion:** The results of this analysis demonstrate sleep duration is related to markers of cardiometabolic health and intermediate CVD risk, but that sleep duration does not independently predict incident CVD. These findings may be explained by the interdependence of 24-hour activities, including sleep duration, and their relationship to cardiometabolic health. While results do not support sleep duration as a risk factor for CVD, they do support sleep duration as a lifestyle behavior worth targeting for cardiometabolic risk reduction in older women. To better understand how sleep relates to cardiometabolic health, we must better understand the interdependence and interrelationships of activities throughout the 24-hour day.

## INTRODUCTION

The aging population in the United States (US) is in a period of rapid growth. By 2050, the population over the age of 65 will surpass 80 million, doubling in size from 2010.<sup>1</sup> Not only are more adults entering the demographic group defined as older adult, but within this population, older adults are also living longer.<sup>1</sup> In line with the growing older adult population, there has been an increase in the focus on the promotion of healthy aging and aging research. Current aging research is focused on understanding the public health burden of chronic diseases, the changing definition of disability, and the use of medical care associated with the growing healthcare needs of this population. It is estimated that over 80% of the older adult population have at least one chronic disease, and almost 30% of these have two chronic conditions. With each chronic condition the costs associated with medication use and medical care increases. In the next decade, research focused on reducing the prevalence and burden of chronic conditions in the aging population through lifestyle behavior modification is critical.<sup>2,3</sup>

Cardiovascular Disease (CVD) is the most prevalent chronic disease in the aging population.<sup>2</sup> According to the American Heart Association, CVD is a disease of the heart or blood vessels, including heart attack, stroke, arrhythmia, and heart valve problems.<sup>4</sup> In the US, CVD is the leading cause of death, accounting for 1 in 4 deaths; approximately 10,000 deaths annually.<sup>5</sup> Over the course of the last 50 years, CVD mortality rates in the US have decreased across every population subgroup.<sup>6</sup> Despite the overall reduction in deaths, CVD is still a significant public health problem. Advances in CVD prevention have reduced the number of CVD deaths overall, however in the last decade CVD deaths in females have exceeded those in males.<sup>7,8</sup> For women, CVD is responsible for more deaths than all forms of cancer combined.<sup>9</sup> Older women over the age of 80 years are at greatest risk for CVD, with higher incidence of

CVD events than their male counterparts.<sup>5</sup> Rates of CVD prevalence and mortality differ across racial-ethnic subgroups of women. African American women have higher rates of CVD, CVD mortality, and CVD risk than any other racial/ethnic subgroup.<sup>8-10</sup> In the US, nearly half of African American women are currently living with CVD.<sup>8</sup> Much less is known about the rates of CVD in Hispanic/Latino, Asian American, and American Indian women.<sup>11</sup> Overall, The American Heart Association estimates that more than one in three US women has some form of CVD, and an additional 90% of women are currently living with one or more risk factors.<sup>9</sup>

There are a number of modifiable risk factors that increase an individual's risk for developing CVD including: obesity, elevated total cholesterol, reduced HDL cholesterol, diabetes, hypertension, and elevated high-sensitivity C-reactive protein (CRP).<sup>9</sup> Additionally, lifestyle behaviors such as smoking, poor diet, lack of physical activity (PA), and sedentary behavior (SB) have been identified and shown to increase a women's risk of developing CVD and developing CVD risk factors.<sup>5,7,9</sup> Epidemiologic studies predict that the prevalence of these risk factors will only continue to increase for women in the US population.<sup>12,13</sup> As the prevalence of CVD and CVD risk factors increase in the US population, it is apparent that more research is needed to identify risk factors that can be modified and targeted for lifestyle interventions.

Poor or insufficient sleep is a potential CVD lifestyle risk factor worthy of greater exploration. Hours spent sleeping account for more than 30% of daily behavior.<sup>12</sup> Recently, sleep has gained public health attention as a modifiable behavior related to various chronic health conditions. Research has included a focus on the cardiometabolic effects of poor or insufficient sleep, including a number of cross-sectional and prospective studies demonstrating that self-reported sleep duration is a predictor of incident cardiometabolic conditions such as: type 2 diabetes, hypertension, and obesity (Table I.1).<sup>13-33</sup> In addition to the large number of studies



examining the association between sleep duration and CVD risk factors, longitudinal studies have found that self-reported sleep duration was independently associated with an increased risk of CVD events and CVD mortality (Table I.2).<sup>34-43</sup> Meta-analyses of the existing research have concluded that inadequate sleep duration and poor sleep quality are associated with increased development, progression, and severity of CVD and CVD comorbidities.<sup>10</sup>

Specifically for older adults, there is even greater evidence supporting sleep duration as a risk factor for CVD. As risk of CVD increases with age, so does the risk of experiencing inadequate sleep durations and poor sleep quality. Over half of older adults in the US regularly report experiencing disturbed sleep.<sup>44</sup> Age-related changes in sleep include shorter or longer total sleep time (TST), increased frequency of awakenings, difficulty maintaining sleep, decreased sleep efficiency, and changes to sleep architecture.<sup>44-48</sup> While these age-related changes in sleep are common among older adults, evidence suggests that post-menopausal women experience more difficulty adapting to these changes. Older women are more likely to report poor sleep quality, sleep disturbances, and nocturnal awakenings than their male counterparts.<sup>44,46,48</sup> If sleep duration is a risk factor for the development and progression of CVD, the large proportion of older adult women who regularly experience short or long sleep are at risk and pose a significant public health concern.<sup>49</sup> There is a need for research to examine the relationship between sleep duration and CVD risk in an older population of women, and to determine if insufficient sleep duration, above and beyond physical inactivity, is a CVD risk factor worthy of further examination.

Besides pharmacological intervention, cardiovascular prevention strategies for women focus on the reduction of CVD risk through the promotion of a healthy lifestyle. Current lifestyle interventions have primarily focused on smoking cessation, increasing daily minutes of PA and

maintaining a well-balanced diet.<sup>5,50</sup> Objectively measured PA, using accelerometers, has shown to independently have beneficial associations with cardiometabolic health and be protective against incident CVD.<sup>51,52</sup> For women, increases in daily minutes of PA decrease CVD risk,<sup>53</sup> however the results of many PA interventions have shown only moderate increases in PA among women.<sup>54</sup> For older women, meeting PA intervention targets is even more difficult to achieve. In fact, estimates show that <10% of participants adhere to prescribed lifestyle treatment and intervention guidelines.<sup>50</sup> The disparities in the high incidence and prevalence of CVD and CVD risk factors specifically in women and subgroups of women, suggest that current prevention strategies are not effective for these populations. To improve upon current approaches to CVD prevention for women, the AHA has funded a Strategically Focused Research Network of 5 centers who will receive \$15 million dollars and are committed to advancing research of CVD prevention in women. One of the SFRN centers is focused on exploring SB as a CVD lifestyle intervention target. SB interventions may hold more promise for women, when PA targets are not achievable. Laboratory studies have shown breaks in sedentary time, even more than PA bouts, were related to meaningful decreases in biomarker-measured CVD risk.<sup>55,56</sup> A population based study demonstrated that a 1-2 hour reduction in sedentary time was related to substantial reductions in CVD risk.<sup>57</sup> New research studies targeting reductions in daily SB have achieved large reductions in sitting time, including in older adults, and have shown the independent health impacts of SB while adjusting for PA.<sup>58</sup> The potential success of the SB interventions not only demonstrates the need to explore novel lifestyle risk factors, beyond PA, that may be more achievable and more effective in decreasing CVD risk among women, but also that we must consider that behaviors do not occur in isolation and are a part of the finite 24-hour day. The majority of current CVD lifestyle interventions have targeted changing one behavior without

considering the impact this will have on the other behaviors that make up the 24-hour day, including sleep.

Thus far, sleep intervention studies has been limited in number, size, and scope and have not been designed to directly target CVD prevention in women. Clinical experimental studies focused on altering sleep duration have been primarily concerned with the impact of restricting sleep duration on energy intake (diet), energy expenditure, or on markers of insulin resistance and inflammation.<sup>59</sup> These studies are more focused on the mechanistic pathways through which sleep may be related to weight gain, metabolism, and markers of cardiovascular health and therefore have been small in sample size, limited in generalizability, and short-term in length. There is a need for research designed to assess the longer-term impact of sleep duration interventions, with the inclusion of women, older adults, and other underrepresented population subgroups.<sup>59</sup> Further, more research is needed to determine if sleep duration, independent of other 24-hour activity, should be considered an intervention target for CVD lifestyle interventions for women.

Overall the aim of this thesis is to assess if sleep duration is independently associated with cardiometabolic health and if insufficient sleep duration is a risk factor that contributes to the development of CVD in older women. This thesis will leverage the rich and unique OPACH study dataset. “Objective Physical Activity and Cardiovascular Health” (OPACH) was a funded ancillary study to the Women’s Health Initiative (WHI) Long Life Study. The NHLBI-Long Life Study was an extension study of the WHI-observational cohort and was conducted between 2012-2013. Women were recruited from 40 clinical centers across the US. The study included 7875 women between the ages of 63-99 from previous WHI cohorts. With the purpose of having a race/ethnicity diverse study sample, the Long Life Study purposefully oversampled

to compile a cohort that was 48% white, 35% African-American, and 17% Hispanic. The objective of the OPACH study was to examine CVD and accelerometer-measured PA in older adult women. The consented OPACH sample included 7048 women. While the primary aim of the OPACH study was focused solely on PA, 24-hour activity data was collected. In addition to accelerometer-measured 24-hour activity data, the OPACH study includes measures of physical functioning, lifestyle questionnaires, and clinical biomarkers. Participants were contacted yearly to provide updated medical history including self-report of CVD events with follow-up up to 5 years.

This thesis aims to build upon the existing research on sleep duration and CVD risk in women, and to further contribute to the scientific evidence by addressing some of the gaps in the current literature. Figure I.1 depicts the aims of three chapters and the relationships assessed in this thesis.

Chapter 1 contributes to the existing research on sleep duration and CVD risk by providing an in-depth analysis of the relationship between accelerometer measured sleep duration and markers of cardiometabolic health. The aim of chapter 1 is to assess if sleep duration, measured with accelerometers, is associated with numerous cardiometabolic markers, including measures of insulin resistance, inflammation, body composition, and cardiovascular health in older women. As outlined in Table I.1, the majority of research examining the relationship between sleep duration and cardiometabolic health has used self-reported measures of sleep duration. Further, the relationship between sleep duration and CVD risk factors have not been sufficiently examined in racial-ethnically diverse samples of older women. This chapter provides a significant contribution by using accelerometer-measured sleep in a diverse cohort of older women to examine how sleep duration is related to cardiometabolic health. Additionally, in

this analysis novel isotemporal modeling techniques are used to explore the interrelationship of sleep duration with the other 24-hour day activities that are related to cardiometabolic health, including PA and SB. These analyses will contribute significantly to understanding not only how sleep duration, but 24-hour activity is related to cardiometabolic health in older women and will be one of the first analyses to do so using rigorously processed 24-hour accelerometer data with accelerometer measured sleep duration.

Building on the assessment of sleep duration and markers of cardiometabolic health, Chapter 2 is an examination of the relationship between sleep duration and a clinically relevant CVD risk score, the Reynolds Risk Score (RRS); used clinically to predict 10-year risk of CVD.<sup>60</sup> Previously the relationship between self-reported sleep duration and individual CVD risk factors has been examined, with reviews and meta-analyses compiling data to draw conclusions about overall cardiometabolic risk.<sup>10,35,61,62</sup> While examining CVD risk factors individually may explain the relationship between sleep and cardiometabolic health, they may not explain the relationship between sleep and overall CVD risk. Further, in the clinical setting, composite risk factor scores are valuable to predict overall CVD risk and to help decide need for further testing (e.g. stress testing, coronary calcium measurements). This chapter is one of the first analyses to include accelerometer measured sleep duration and a composite CVD risk factor score to examine sleep duration and estimated CVD risk in older women.

In Chapter 3, the relationship between cardiovascular events over 3-5 years of follow-up and two different methods to estimate sleep duration is examined. This chapter includes one of the first prospective studies to examine the association between accelerometer-measured sleep duration and incident CVD. Further, previous studies have assessed self-reported sleep duration and CVD events. This analysis includes both self-reported sleep duration and accelerometer-

measured sleep duration in the same diverse cohort of older women and is able to draw comparisons between the two measures. Chapter 3 will fill an existing gap in the literature as one of the first studies to assess the relationship between sleep duration and incident CVD using an objective measure of sleep duration, as well as providing insight on how the relationship between sleep duration and CVD risk differs by different methods to estimate sleep duration. This study will provide much needed evidence on the relationship between sleep duration and incident CVD in older women.

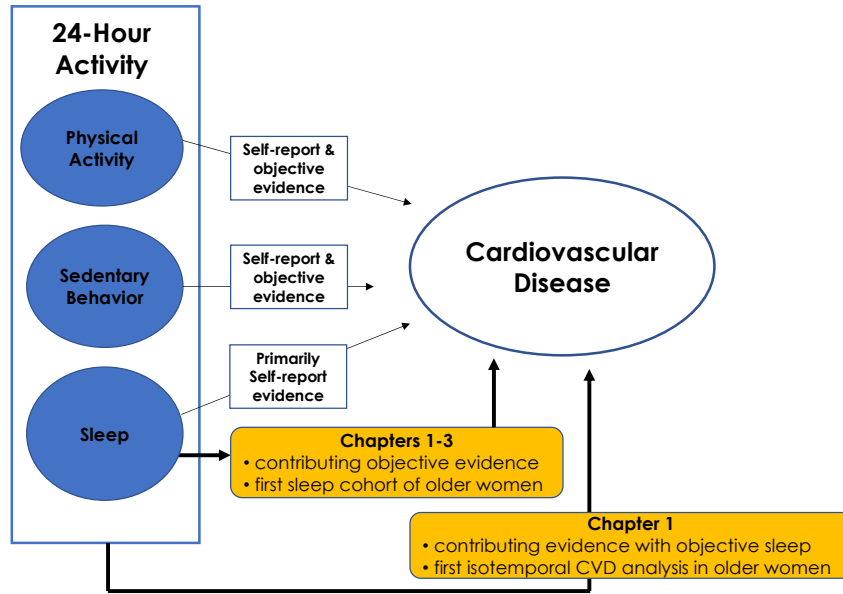
There are many limitations in the existing scientific evidence of the link between sleep duration and cardiovascular health. This thesis aims to address these gaps to advance our understanding of the role that sleep duration plays in CVD development in older women. First, many of the existing epidemiologic studies have relied on self-reported sleep duration from 1 or 2 survey items that ask a question similar to: “How many hours of sleep do you usually get a night?”<sup>14,61,63</sup> A previous validation study comparing self-reported sleep duration to wrist actigraphy in a sample of over 600 adults indicated self-report is usually an overestimate of sleep duration, is only moderately correlated to objectively measured sleep duration ( $r=0.47$ ), and has a systematic bias across social-demographic characteristics.<sup>63,64</sup> Studies that have used objective measures of sleep duration have found different results in the associations between sleep duration and cardiometabolic risk factors, with some studies showing no significant associations.<sup>20,26,28,30,32</sup> Additionally, previous study samples primarily consisted of middle-aged non-Hispanic white adults. While CVD incidence is higher in older women, and African American and Non-white Hispanic populations,<sup>5</sup> most published studies on sleep and CVD risk have not adequately included women with broad representation from these groups.<sup>10,59</sup> This is a concern as evidence suggests that sleep duration and quality differs across age groups and

racial/ethnic groups.<sup>47,65</sup> According to the American Heart Association, inclusion of these understudied populations, including aging women and African American and Non-white Hispanic women, and the objective assessment of sleep, should be high priorities for future research.<sup>59</sup> Lastly, based on the growing evidence that demonstrates the interrelationships of daily activities, it is important we move beyond the paradigm of considering activities in isolation. To better understand the relationship between sleep duration and CVD, we must also account for how daily PA may influence this relationship. This thesis will leverage the 24-hour activity data to account for daily PA and SB in the relationship between sleep duration and CVD. This additional step has rarely been included in previous sleep and cardiovascular health studies.

In summary the purpose of this dissertation is to build upon the existing research on sleep and cardiovascular health in older women. By using accelerometer-measured sleep duration collected in a large and diverse cohort of older women, and through the application of analytic approaches that take into consideration how sleep is part of the 24-hour day, this dissertation is a much needed contribution to existing scientific evidence. In this dissertation, accelerometer-measured sleep duration has been examined in relationship to markers of cardiometabolic health, 10-year estimated risk of CVD, and CVD events. The results of this dissertation will fill gaps in the existing evidence base and will inform lifestyle intervention strategies for CVD prevention. Further, as the popularity of 24-hour data collection increases with the advancement of research activity measurement devices, considering the contribution of sleep to the 24-hour day is not only relevant, but imperative to improving how we approach CVD prevention. The growing older adult population warrants renewed focus on feasible and effective CVD prevention strategies for older adult women. The results of this dissertation will provide an extensive

analysis of the role sleep duration plays in cardiometabolic health and CVD risk and will provide insights for future lifestyle CVD prevention strategies for older women.





**Figure I.1:** Conceptual model for 24-hour heart health dissertation

Table I.1: Summary of literature examining sleep duration and cardiovascular disease risk factors

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
<a href="#">Avax (2003)</a> <sup>19</sup>	A prospective study of self-reported sleep duration and incident diabetes in women ( <a href="#">Nurses Health Study</a> )	Prospective; 10 years follow-up	70,026	43-65 years; all women	Self-reported sleep duration	<b>Diabetes:</b> self-reported diagnosis and follow-up diagnostic tests	RR for diabetes incidence: for short sleep duration of <5 hours 1.57 [1.28-1.92] and for long sleep duration >9 hours 1.47 [1.19-1.80]
<a href="#">Bakker (2015)</a> <sup>20</sup>	Associations between obstructive sleep apnea, sleep duration, and abnormal fasting glucose: the Multi-Ethnic Study of Atherosclerosis (MESA)	Cross-sectional	2,151	45-84 years; 54% women	Polysomnography and wrist actigraphy	Fasting glucose measured; <b>abnormal fasting glucose</b> defined as >100 mg/dl	After considering OSA, sleep duration was not associated with abnormal fasting glucose; increased OR for abnormal fasting glucose for African Americans (OR: 2.14, [1.12-4.08]) and White participants (OR: 2.85, [1.20-6.75]) with OSA
<a href="#">Beihl (2009)</a> <sup>21</sup>	Sleep duration as a risk factor for incident type 2 diabetes in a multiethnic cohort	Prospective; 5 years follow-up	900	40-69 years; 56% women	Self-reported sleep duration	<b>Diabetes:</b> Insulin sensitivity by glucose tolerance test	OR for incident diabetes: 2.36 [1.21- 3.79] for sleep duration < 7 hours compared to 8 hours
<a href="#">Cappuccio (2009)</a> <sup>14</sup>	Quantity and quality of sleep and incidence of type 2 diabetes	Meta-analysis 4.2-32 years	107,756 (13 cohorts)	19-86 years	Self-reported sleep duration	<b>Diabetes:</b> multiple methods	Short and long sleep predicted diabetes incidence: RR: 1.28 [1.03-1.60] in short sleepers; RR: 1.48 [1.13-1.96]
<a href="#">Chaput (2007)</a> <sup>15</sup>	Short sleep duration is associated with reduced leptin levels and increased adiposity; results from	Cross-sectional	740	21-64 years; 56% women	Self-reported sleep duration	<b>BMI:</b> measured height and weight plasma leptin	OR for overweight/obesity: 1.38 [0.89-2.10] in 9-10 hour sleepers; OR 1.69 [1.15-2.39] in 5-6 hour sleepers

**Table I.1:** Summary of literature examining sleep duration and cardiovascular disease risk factors (continued)

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
Chaput (2013) <sup>16</sup>	Short sleep duration as a risk factor for the development of the metabolic syndrome in adults	Prospective; 6 years follow-up	293	18-65 years;	Self-reported sleep duration	MetS based on markers	RR for incident metabolic syndrome: 1.74 [1.05- 2.72] for sleep duration < 6 hours compared to 7-8 hours
Ford (2014) <sup>22</sup>	Sleep duration and body mass index and waist circumference among U.S. adults	Cross-sectional	13,742	mean 46 years; 50% women	Self-reported sleep duration	BMI: measured height, weight, waist circumference	Sleep duration <7 associated with BMI p<0.001) and waist circumference (p<0.001) when compared to 7-9 hours
Gangwisch (2005) <sup>23</sup>	Inadequate sleep as a risk factor for obesity: analysis of NHANES I	Cross-sectional and Prospective	9,588 cross-sectional; 8,073 and 6981 for longitudinal	32-86 years; ~50% women	Self-reported sleep duration	BMI: measured height and weight, self-reported height and weight	In 32-49 year olds, there was significant difference between sleep duration categories and obesity status with <7 hours more likely to be obese; no association for 50-86 year olds; across NHANES waves as sleep duration increased mean BMI values decreased (not statistically significant)
Gangwisch (2006) <sup>18</sup>	Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey	Prospective; 8-10 years follow-up	4810	32-86 years; ~60% women	Self-reported sleep duration	Self-reported blood pressure/ history of hypertension	HR for hypertension: HR:2.10 [1.58-2.79] for sleep duration <5 hours and HR 1.54 [1.03- 2.30] for sleep duration >9 compared to 7-8 hours
Gangwisch (2007) <sup>17</sup>	Sleep duration as a risk factor for diabetes	Prospective; 8-10 years follow-up	8,992	32-86 years; ~60% women	Self-reported sleep duration	Diabetes: self-reported physician	OR for incident diabetes: 1.47 [1.03- 2.09] for sleep duration

**Table I.1:** Summary of literature examining sleep duration and cardiovascular disease risk factors (continued)

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
Gottlieb (2005) <sup>24</sup>	Associations of sleep time with Diabetes Mellitus and impaired glucose tolerance (Sleep Heart Health Study)	Cross-sectional	1,486	53-93 years; 51% women	Self-reported sleep duration	Diabetes: serum glucose level >126 mg/dL, fasting: impaired glucose tolerance: >140 mg/dL and <200 mg/dL	OR for incident diabetes: 2.51 [1.57- 4.02] for sleep duration < 5 hours; OR 1.79 [1.08 - 2.96] for sleep duration >9 hours
Jean-Louis (2014) <sup>25</sup>	Associations between inadequate sleep and obesity in the US adult population: analysis of the national health interview survey (1977-2009)	Cross-sectional	Cross-sectional samples	~42 years; ~50% women	Self-reported sleep duration	BMI: calculated from self-reported height and weight	<5 hours, 30% greater odds of overweight or obesity; 5-6 hours, 20% greater odds of overweight or obesity compared to 7-8 hours. >8 hours had 20% greater odds of being obese
Kim (2016) <sup>26</sup>	Associations between actigraphy-assessed sleep, markers, and insulin resistance in the Midlife Development in the United States (MIDUS) study	Cross-sectional	374	34-83 years; 63% women	Wrist actigraphy	Fasting measures: HbA1c, glucose, insulin, CRP, IL-6, HOMA-IR calculated	In univariate models, short sleep duration associated with insulin resistance and inflammation. In fully adjusted models, no association between sleep duration and insulin resistance or inflammation
Knutson (2006) <sup>13</sup>	Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus	Cross-sectional	161	57 years; 73% women	Self-reported sleep duration	Diabetes defined by HbA1c medical chart review	Short sleep durations associated with higher HbA1c (r=0.27, p<.01)
Knutson (2009) <sup>27</sup>	Association between sleep and blood pressure in midlife	Cross-sectional; Prospective	578	33-45 years	Wrist actigraphy	Blood pressure measured in clinic	Short sleep duration predicted higher SBP and DBP (p<0.05)

**Table I.1:** Summary of literature examining sleep duration and cardiovascular disease risk factors (continued)

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
Knutson (2011) <sup>28</sup>	Cross-sectional associations between measures of sleep and markers of glucose metabolism among subjects with and without diabetes: The CARDIA sleep study	Cross-sectional	155; 40 with diabetes	mean 45 years; 57% women	Wrist actigraphy	fasting insulin and glucose values	In subjects without diabetes: no association between sleep measures and glucose, insulin, or HOMA-IR. In subjects with diabetes: association between sleep quality measures and higher insulin, glucose, and HOMA-IR values
Lauderdale (2009) <sup>29</sup>	Cross-sectional and longitudinal associations between objectively measured sleep duration and body mass index: CARDIA Sleep Study	Cross-sectional; Prospective	612	mean 45 years; 57% women	Wrist actigraphy	BMI: measured height and weight	In cross-sectionally analysis, short sleep duration and sleep fragmentation associated with higher BMI (p<0.05). No longitudinal association between sleep and changes in BMI
Matthews (2011) <sup>30</sup>	Associations of Framingham risk score profile and coronary artery calcification with sleep characteristics in Middle-aged Men and Women: Pittsburg SleepSCORE study	Cross-sectional	224	45-75 years; 50% women; 43% Afr. Am.	Wrist actigraphy and polysomnography	Framingham risk score assessments for anthropometrics, resting blood pressure, and lipid profiles	Higher Framingham risk score profiles (high vs low) had significantly shorter sleep (PSQI). No significant difference found by actigraphy measured sleep duration.
Miller (2009) <sup>31</sup>	Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation:	Cross-sectional	4,642		Self-reported sleep duration	Inflammatory markers: Interleukin-6 (IL-6) and high-sensitivity-CRP	Relationships varied between men and women. No association in men. In women, relationship for IL-6 appeared to be linear, for CRP appeared to be non-linear.

**Table I.1:** Summary of literature examining sleep duration and cardiovascular disease risk factors (continued)

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
Montag (2017) <sup>32</sup>	Association of sleep characteristics with cardiovascular and metabolic risk factors in a population sample: the Chicago Area Sleep Study	Cross-sectional	492	35-64 years	Wrist actigraphy	<p><b>Hypertension:</b> measured BP, hypertension defined as SBP &gt;140 mm Hg, DBP&gt;90 mm Hg</p> <p><b>obesity:</b> measured height and weight obesity defined as &gt;30 kg/m<sup>2</sup></p> <p><b>diabetes:</b> fasting glucose and HbA1c values</p>	<p>Sleep duration was not associated with any cardiovascular risk factor.</p> <p>Sleep fragmentation and self-reported sleep quality increased OR for hypertension</p>
Patel (2006) <sup>33</sup>	Association between reduced sleep and weight gain in women (Nurses Health Study)	Prospective; 16 years	68,183	30-55 years; 100% women	Self-reported sleep duration	<p><b>BMI:</b> self-reported height and weight; obesity defined as &gt; 30 kg/m<sup>2</sup></p>	<p>Obesity RR: 1.15 [1.04-1.26] for sleep duration of 5 hours; RR:1.06 [1.01-1.11] for sleep durations of 6 hours; similar significant results for 15kg weight increase</p>

**Table I.2:** Summary of literature examining sleep duration and incident cardiovascular disease

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
Ayas (2003) <sup>34</sup>	A prospective study of self-reported sleep duration and Coronary Heart Disease in women (Nurses Health Study)	Prospective; 10 years follow-up	71,617	45-65 years; all women	Self-reported sleep duration	<b>Incident CHD:</b> non-fatal MI or fatal CHD, questionnaire and medical chart review	RR for CHD incidence: for short sleep duration of <5 hours: 1.39 [1.05-1.84] and for long sleep duration >9 hours: 1.37 [1.02-1.85] compared to 8 hours of sleep
Cappuccio (2011) <sup>35</sup>	Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies	Meta-analysis; 6.9-25 years	474,684	31-85 years	Self-reported sleep duration	<b>Incident CHD, stroke, or CVD:</b> Death or non-fatal from death certificate or medical chart review	RR for CHD incidence: for short sleep duration was 1.48 [1.22-1.80] and for long sleep duration was 1.38 [1.15-1.66]. RR for total CVD: for short sleep duration was 1.03 [0.93-1.15] and for long sleep duration was 1.41 [1.19-1.68]
Chen (2008) <sup>36</sup>	Sleep duration and risk of ischemic stroke in postmenopausal women (Women's Health Initiative)	Prospective; 7.5 years follow-up	93,175	50-79 years; All women 83% white	Self-reported sleep duration	<b>Incident Stroke:</b> self-report questionnaire, and medical chart review	RR for incident stroke: for short sleep duration of <6 hours of 8 hours: 1.14 [0.97-1.33], sleep duration of 8 hours: 1.24 [1.04-1.47] and for long sleep duration of >9 hours: 1.70 [1.32-2.21] compared to 7 hours of sleep

**Table I.2:** Summary of literature examining sleep duration and incident cardiovascular disease (continued)

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
Hoovenar-Bloom (2013) <sup>37</sup>	Sufficient sleep duration contributes to lower cardiovascular disease risk in addition to four traditional lifestyle factors: the MORGEN study	Prospective; 10-14 years	17,887	20-65 years; 54% women	Self-reported sleep duration	<b>CVD morbidity and mortality:</b> ascertained through national registries	HR for sufficient (>7 hours) sleep duration 0.57 [0.39-0.83] compared to <7 hours
Rod (2014) <sup>38</sup>	The joint effect of sleep duration and disturbed sleep on cause-specific mortality: results from the Whitehall II Cohort study	Prospective; 22 years	9,098	35-55 years; 33% women	Self-reported sleep duration	<b>CVD mortality:</b> death certificate review	HR for CVD mortality: In women, short sleep (<6 hours) was 1.81 [1.05-3.10] compared to women who slept 7-8 hours
Sands-Lincoln (2013) <sup>39</sup>	Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's Health Initiative	Prospective; 10.3 years	86,329	50-79 years; All women; 80% white	Self-reported sleep duration	<b>Incident CHD and incident CVD:</b> self-report questionnaire, and medical chart review	HR for incident CHD: short sleep <5 hours 1.25 [1.13-1.37] and long sleep >10 hours 1.43 [1.03-1.99] after minimal adjustment. Associations attenuated and no longer significant after further adjustment. Same results for incident CVD
Shankar (2008) <sup>40</sup>	Sleep duration and coronary heart disease mortality among Chinese adults in Singapore: a population-based cohort study	Prospective	58,044	45-74 years; 56% women	Self-reported sleep duration	<b>CHD mortality:</b> death registry	RR for incident CHD: short sleep <5 hours was 1.57 [1.32-1.88] and for long sleep duration >9 hours was 1.79 [1.48-2.17] compared to sleep durations of 7 hours



**Table I.2:** Summary of literature examining sleep duration and incident cardiovascular disease (continued)

Author (Year)	Title	Study Design	Sample (N)	Sample Age (y) % women	Exposure Variable Assessment	Outcome Variable Assessment	Results
Shankar (2010) <sup>41</sup>	Insufficient rest or sleep and its relation to cardiovascular disease, diabetes, and obesity in a national, multiethnic sample (BRFSS)	Cross-sectional	372,144	>25 years; 50% women	Self-reported insufficient sleep	Physician diagnosed CVD: self-reported	OR for any CVD: for those reporting 30 days of insufficient sleep was 1.67 [1.55-1.79] when compared to 0 days of insufficient sleep
Strand (2016) <sup>42</sup>	Self-reported sleep duration and coronary heart disease mortality: a large cohort study of 400,000 Taiwanese adults	Prospective; 17 years	392,164	>20 years	Self-reported sleep duration	CVD mortality: death registry	HR for CHD mortality: for short sleep duration (<4 hours) was 1.34 [0.87-2.07] and for long sleepers (>8 hours) was 1.35 [1.11-1.65] when compared to 6-8 hour sleep duration
Yang (2016) <sup>43</sup>	Longer sleep duration and midday napping are associated with a higher risk of CHD incidence in middle-aged and older Chinese: the Dongfeng-Tongji cohort study	Prospective; 5 years	19,370	Mean 62.8 years; 56% women	Self-reported sleep duration	Incident CHD: non-fatal MI or fatal CHD, questionnaire and medical chart review	HR for incident CHD: no relationship in short sleepers (<6 hours) and in long sleep durations (>10 hours) HR was 1.33 [1.10-1.62]

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## CHAPTER 1

### Modeling the Cardiometabolic Benefits of Sleep in Older Women:

#### Exploring the 24-Hour Day

##### ABSTRACT

**Background:** Activities throughout the 24-hour day, including sleep, sedentary behavior (SB), and physical activity (PA) have been associated with cardiometabolic health. Few studies have examined the relationship between accelerometer-measured 24-hour activity and cardiometabolic risk factors. Sleep extension may be a feasible cardiovascular intervention strategy; however, more research is needed to understand of what activity from within the 24 hour day additional sleep should displace.

**Methods:** Women from the Objective Physical Activity and Cardiovascular Health Study (N=3329; mean age 79.05 years) wore ActiGraph GT3X+ accelerometers on the hip for 24 hours and completed a daily sleep log. Sleep data were scored according to a standard protocol using the sleep logs. Adjusted regression models estimated the relationship between sleep duration and cardiometabolic markers. Stratified by sleep duration (<8 hours, >8 hours), isothermal models were run across to estimate the association with cardiometabolic markers of reallocating daytime activity time (SB, light PA (LIPA), moderate to vigorous (MVPA)) to or from sleep.

**Results:** After adjustment, sleep duration was significantly related to insulin, C-reactive protein, insulin resistance, glucose, total cholesterol, triglycerides, waist circumference, and 10-year estimated CVD risk. For short sleepers, reallocating one standard deviation (33 minutes/day) of MVPA to sleep was detrimental across all cardiometabolic markers. Similar detrimental associations were observed when LIPA (74 minutes/day) was reallocated to sleep. Reallocating one standard deviation of SB (91 minutes/day) to sleep had small beneficial



associations with some of the cardiometabolic markers. In long sleepers, reallocating time from sleep to MVPA or LIPA had beneficial associations.

**Conclusions:** In older women, there was a significant relationship between sleep duration and cardiometabolic risk factors. Results from isotemporal models indicate possible risks and benefits of reallocating time to or from sleep to lower cardiometabolic risk, but results must be confirmed in randomized clinical trials.

## INTRODUCTION

Throughout the 24-hour day, time is spent in activities that can be distinctly categorized as sleep, sedentary behavior, or physical activity (light physical activity and moderate to vigorous physical activity). Individually, these 24-hour activities are linked to cardiometabolic health. Objectively measured physical activity (PA), both moderate to vigorous (MVPA) and light intensity (LIPA) have been shown to have beneficial associations with cardiometabolic health including reduced risks of incident cardiovascular disease (CVD).<sup>1,2</sup> Objectively measured sedentary behavior (SB) has detrimental associations with markers of cardiometabolic health and has been associated with increased risk of incident CVD, even after adjusting for PA.<sup>3-6</sup> Self-reported short sleep durations (<7 hours) predict incident cardiometabolic conditions such as: type 2 diabetes, obesity, and cardiovascular events.<sup>7-12</sup> Only a few cross-sectional studies have used wearable sensors to examine associations between objectively measured sleep duration, both short and long, and modifiable cardiometabolic risk factors, including cardiovascular biomarkers (such as glucose and C-reactive protein), systolic blood pressure, and obesity.<sup>13-17</sup>

Despite the growing research on the relationship between sleep duration and cardiometabolic health, epidemiologic studies show that over 30% of Americans are not getting the recommended 8 hours of sleep per night.<sup>18</sup> For older women, reports of poor or disturbed sleep are higher than for men.<sup>19</sup> Age-related changes in sleep lead to more frequent reports of poor sleep quality, restless sleep, and more nocturnal awakenings.<sup>20-23</sup> Focusing on extending or decreasing sleep time for cardiometabolic risk reduction may be an interventional strategy worth exploring for aging women. Recent evidence suggests that sleep extension interventions may be a feasible strategy to reducing CVD risk.<sup>18,24</sup>

The high incidence and prevalence of CVD among older women in the United States suggest that current cardiovascular prevention strategies may not be completely effective for aging women. Many existing lifestyle interventions focus on increasing daily PA. However, it is estimated that only 10-30% of older adults currently meet PA guidelines of 30 minutes of daily MVPA.<sup>25,26</sup> Sleep extension interventions may be a more feasible alternative to PA interventions particularly in older populations where PA may be difficult to achieve due to health or environmental barriers. Additionally, new research on daily SB reduction holds promise as large reductions in sitting time have been achieved.<sup>27</sup> As clinical recommendations and sleep research support increasing sleep time, more research is needed to understand from where in the 24-hour day that time should come. Would it be beneficial if participants reduce sitting time to increase sleep time? Further, it is not clear whether it is more beneficial to increase a behavior like PA, or if it also results in less sleep time.

Recently, researchers have used Isotemporal Substitution Modeling<sup>28</sup> to estimate the change in cardiometabolic risk if a fixed amount of time spent in one activity is shifted to another activity. Several of these studies have demonstrated that the way time is allocated to daily activities is significantly related to cardiometabolic health.<sup>29-31</sup> Previous isotemporal analyses have focused on daytime activity and most have not included sleep in their analyses. The isotemporal studies that did include sleep relied solely on self-reported sleep measures.<sup>28-32</sup>

The primary aim of this study was to use 24-hour accelerometry data to: (1) examine the associations between objectively measured sleep duration and markers of cardiometabolic health; and (2) construct isotemporal substitution models to assess the cardiometabolic associations of redistributing time to or from sleep, when it is shifted to or from another activity. This study differs from the isotemporal approaches previously taken, by including objectively measured

sleep duration and focusing specifically on reallocating time to or from sleep duration. This modeling will answer the questions: What is the benefit on cardiometabolic risk of increasing sleep duration, in short sleepers, if time spent in SB is decreased? Or what is the benefit of decreasing sleep duration, in long sleepers, if time spent in LIPA or MVPA is increased? This study will provide a better understanding of how 24-hour activity is related to cardiometabolic health and may highlight opportunities to develop more feasible cardiovascular lifestyle interventions which could be tailored to older adults' capacity for behavior change.

## **METHODS**

### ***Study Sample***

Our study population included older women enrolled in the Objective Physical Activity and Cardiovascular Health (OPACH) study, an ancillary study to the Women's Health Initiative Long Life Study aimed at examining the relationship between accelerometer-measured physical activity and incidence of CVD in older women (ages 63-99 years). More detailed information on the OPACH study objectives, recruitment, and methodology are published.<sup>33</sup> Participants were consented for participation in the OPACH study (N=7048) between 2012-2013 and in-home visits were conducted to obtain fasting blood draws, health and lifestyle questionnaires, anthropometric measurements, and blood pressure readings. At the home visit, participants received a GT3x accelerometer, instructed to wear the device on their waist for 24 hours per day, and asked to complete a daily sleep log over a 7-day period. Of the consented OPACH participants, 6,489 women returned their device and provided at least one day of accelerometer data; 6,114 of these women also completed sleep logs for at least one day. To be eligible for the present study, women had at least two 24-hour periods of valid accelerometer data, a completed sleep log, and fasting CVD biomarker results (Figure 1.1).

### *Objective 24-Hour Activity*

24-hour activity was assessed with a hip-worn triaxial accelerometer (Actigraph GT3X+; Pensacola, FL). The ActiGraph device, worn on the hip, has been validated for physical activity, sedentary behavior and sleep duration estimates.<sup>34,35</sup> Data were recorded in 1-second epochs at 30 Hertz. After the device was returned, raw data were processed using ActiLife version 6.11 software, separately for sleep duration and the daytime activity variables.

### *Sleep Duration*

The sleep duration data were processed using the raw data condensed to 60 second Agilegraph Data File (AGD) with the low frequency extension filter applied. AGD files were scored using a standard protocol. A trained member of the research team identified the primary sleep window using the participant sleep logs and a visual review of the data for each night the participant wore the device. This procedure is aligned with the Society of Behavioral Sleep Medicine actigraphy methods guidelines and draws from a protocol shown to have high interrater reliability.<sup>36,37</sup> The validated Cole-Kripke algorithm<sup>38</sup> was applied and classified the sleep window, minute by minute, as sleep or wake time. Estimates of nightly sleep duration were derived from the summing of epochs classified as sleep (minutes/night) during the defined in-bed period.

### *Physical Activity and Sedentary Behavior*

PA data were processed as previously described in detail.<sup>33</sup> Age-appropriate PA-intensity cut points were used to classify PA intensity levels,<sup>39</sup> including: light physical activity (LIPA; 19–518 counts/15 s) and moderate-to-vigorous intensity (MVPA;  $\geq 519$ ). SB was defined as less than 19 counts/15 second period. In bed time that was not classified as sleep by the sleep-wake algorithm was defined as SB.

### ***Markers of Cardiometabolic Health***

Resting blood pressure (BP) was measured after a 5-minute rest period using an aneroid sphygmomanometer and cuff size based on measured arm circumference. The average of two BP readings was recorded. Participant height (cm) and weight (kg) were assessed by trained staff using a portable scale and stadiometer. Participants' body mass index (BMI)(kg/m<sup>2</sup>) was calculated with the height and weight obtained at the LLS study visit. Fasting blood samples were sent to the University of Minnesota Fairview Advanced Research and Diagnostic Laboratory (ARDL) for cardiometabolic biomarker testing as previously described.<sup>40</sup> The following markers of cardiometabolic health were included in these analyses: fasting insulin, C-reactive protein (CRP), homeostatic model assessment of insulin resistance (HOMA-IR), fasting glucose, HDL cholesterol, total cholesterol, triglycerides, systolic blood pressure, waist circumference, BMI, and Reynolds Risk Score (RRS),<sup>41</sup> a composite index that estimates 10-year CVD risk.

### ***Covariates***

Participant demographic information, education, smoking, self-rated health, self-reported sleep disturbances, and history of chronic conditions were ascertained with the LLS and WHI lifestyle survey and medical history questionnaires. Self-rated health was derived from 1-item from the WHI lifestyle questionnaire: "In general would you say your health is...". Response options ranged from "excellent" to "poor". The WHI Insomnia Rating Scale (WHIIRS) was used to assess self-reported sleep disturbances.<sup>42</sup> The five item scores (0-4) are summed to create a scale score ranging from 0-20. A higher WHIIRS score is reflective of greater presence of sleep disturbances and has been shown to predict CVD.<sup>43</sup> Self-reported chronic conditions were collected in the baseline LLS survey and were used to create a comorbidity index score. The

index included self-reported history of chronic obstructive pulmonary disease (COPD), osteoarthritis, cerebrovascular disease, cancer, cognitive impairment, and hip fractures. The number of conditions was summed to create a comorbidity index score (0-6). Participants were categorized as having no comorbid conditions (0), 1-2 conditions (1), or more than 2 conditions (2).

### *Statistical Analysis*

Average daily minutes of sleep, PA, and SB were included in a series of regression models to assess the associations with markers of cardiometabolic health. Prior to analyses, all cardiometabolic marker variables were log transformed. All of the activity variables were adjusted for device wear time using the residuals method<sup>44</sup> to account for variation in wear time across individuals that may impact estimates of 24-hour activity categories. Daily activity variables were summed to create a 24-hour total wear time variable. Models included adjustment for age, race/ethnicity, education, sleep disturbances, self-rated health, smoking status and an index of comorbid conditions.

### *Single Variable Models*

Single-variable linear regression models for each marker of cardiometabolic health and each activity were performed and estimated mean values for each cardiometabolic marker were compared according to sleep durations of 6 hours, 8 hours, and 10 hours, adjusting for confounders, but not for the other types of activity. As one of the aims of the current analyses was to examine the effect of reallocation of time to or from sleep duration, the primary focus was on the independent associations of sleep duration with cardiometabolic markers as the first step. The single variable models for MVPA, LIPA, and SB were also performed adjusting for covariates and confounders. Evidence demonstrates that the relationship between sleep duration

and cardiometabolic biomarkers may be U-shaped, with both short and long durations significantly associated with various cardiometabolic biomarkers. A quadratic term was included in the single variable models to explore the possible U-shape in the relationships. When the quadratic term was not significant, it was removed, and the model was rerun with only a linear term for sleep duration to examine the possible linear association.

When significant associations were observed in the single variable sleep models, isotemporal substitution models were performed across the stratified sample (<8 hours, ≥8 hours) to test the reallocation of time to sleep for short sleepers and from sleep for long sleepers.

#### *Isotemporal Substitution Models*

Isotemporal substitution models estimated the association with the cardiometabolic markers of reallocating daytime activity to or from sleep. The substitution model for each cardiometabolic marker included a variable for each daily activity beside sleep duration (SB, LIPA, and MVPA), in addition to the 24-hour total wear time variable. Including a total wear time variable in the model holds time constant and allows interpretations to be made about the cross-sectional associations of cardiometabolic marker levels with reducing the mean time spent in one activity by equivalently increasing the mean time spent in another activity. Not including the sleep variable in the models allows for interpretation of increasing or decreasing sleep time by shifting it from or to another daily activity. Coefficients for each activity were multiplied by one standard deviation of the behavior, to model a one standard deviation reallocation of time.

Interpretation of the Isotemporal models (and the reallocation of time) requires the assumption of a linear relationship among exposure variables and the outcome variables. The median average nightly sleep duration time of 8.17 hours was used to stratify the sample as short (<8 hours) or long (≥8 hours) sleepers. The isotemporal analyses were stratified across the



samples of short (<8 hours) and long ( $\geq$ 8 hours) sleepers to allow for examination of linear associations and proper interpretation if sleep duration was increased for short sleepers or decreased for long sleepers.

Importantly, because these data are cross-sectional, the resulting coefficients cannot be interpreted as causal effects, but as estimated effects from the reallocation of 24-hour time. All analyses were performed R statistical software version 3.1.1.<sup>45</sup>

## **RESULTS**

Of the 6489 women in the OPACH sample with accelerometer data, 4580 had valid sleep data. One hundred and ninety-two had less than 3 complete days of 24-hour wear, and 1059 did not have LSS blood draws, leaving data from 3,329 women available for this analysis. There were statistically significant differences in the age and race/ethnicity distributions between the current analytic study population and those not included from the OPACH study cohort with at least one day of accelerometer data (N=6489). The 3329 women included in the sleep sample were slightly older (mean age: 78.9 vs 78.5 years,  $p<.01$ ), and the included participants had a larger proportion of white women (53% vs 45%), and a smaller proportion of African American women (30% vs 38%,  $p<.001$ ) than the original OPACH sample.

Socio-demographic and health status characteristics of this analytic sample are presented in Table 1.1. Participants had an average age of 78.9 (SD=6.7) years. Over half of the participants were white (53.3%) and college educated (78.9%). Only 2.3% of the sample were currently smokers and 29.3% were classified as obese. Participants self-reported an average sleep disturbance score of 6.3 (SD=4.5) out of 20. The average nightly accelerometer-measured sleep duration for the sample was 490 minutes (SD=72.1) or 8 hours 10 minutes.

Participant characteristics by sleep category are shown in Table 1.1. Women with longer sleep durations (<8 hours) were significantly more likely to be older and white. Additionally, the longer sleepers were more likely to report higher sleep disturbance scores. Women with shorter sleep durations were more likely to be Black or Hispanic and had significantly higher BMIs. Distribution of average minutes of time spent in each daily activity by sleep category are presented in Table 1.2. On average, long sleepers had more minutes of daily wear time, and sleep time, but fewer minutes of MVPA, LIPA, and SB.

Results from the single variable sleep regression models are presented in Table 1.3. In addition to the model results, estimated mean values for each cardiometabolic marker at 6 hours, 8 hours, and 10 hours of sleep are presented. Sleep duration was significantly related to insulin (p: <0.001), HOMA-IR (p: <0.001), glucose (p: <0.05), total cholesterol (p: <0.05), triglycerides (p: <0.001), waist circumference (p: <0.05), and RRS (p: <0.001) in the single variable models. The single variable models adjusted for age, race/ethnicity, education, wear time, sleep disturbances, self-rated health, smoking status, and comorbid conditions. The quadratic term for sleep duration was significant in the CRP (p: <0.05), glucose (p: <0.05), waist circumference (p: <0.05), and RRS models (p: <0.001), suggesting the relationship between sleep duration and these markers is U-shaped, with higher values for both short and long sleep duration. Results of the single variables models for MVPA, LIPA, and SB are presented in Table 1.4. MVPA, LIPA, and SB were all significantly related to every cardiometabolic marker after adjusting for age, race/ethnicity, education, wear time, sleep disturbances, self-rated health, smoking status, and comorbid conditions.

The results of the Isotemporal substitution models for short sleepers and long sleepers are displayed in Figures 1.2 and 1.3. For the short sleepers, model results estimate the association of

reallocating one standard deviation of activity to sleep. For short sleepers, reallocating one SD (33 minutes/day) of MVPA to sleep was detrimental across all cardiometabolic markers. Reallocating 33 minutes/day of MVPA to sleep was significantly associated with higher values of insulin (10%), CRP (4.5%), HOMA-IR(5.5%), glucose (1%), triglycerides (4.6%), waist circumference (1%), and RRS (8%). For LIPA, a similar detrimental association was observed in some markers when one standard deviation of LIPA (74 minutes/day) was reallocated to sleep. Reallocating 74 minutes/day of LIPA to sleep was significantly associated with higher values of insulin (9%), CRP (6%), HOMA-IR (4%), and triglycerides (10%). Conversely, reallocating one standard deviation of SB (91 minutes/day) to sleep had beneficial associations with some of the cardiometabolic markers, including lower values of CRP (9%), waist circumference (1.2%), and RRS (2.6%). Very small beneficial associations were observed for insulin, HOMA-IR, and glucose when 91 minutes/day was reallocated from SB to sleep. Reallocating one standard deviation of LIPA, MVPA, or SB to sleep was detrimentally associated with higher triglyceride values.

In long sleepers, reallocating time from sleep to MVPA (33 minutes/day) had beneficial associations across almost all cardiometabolic markers. Reallocating 33 minutes/day of sleep to MVPA was significantly related to lower values for insulin (10.8%), CRP (6.5%) and HOMA-IR (5.7%) and RRS (9.5%) and slightly lower levels of glucose (1%), triglycerides (1%), waist circumference (1%). Similar results were observed when sleep time was shifted and LIPA was increased by one standard deviation (74 minutes), with lower values for insulin (10.3%), CRP (15%), HOMA-IR (5.5%), glucose (1%), triglycerides (7%), waist circumference (1.2%), and RRS (4.3%). Shifting time from sleep to increase SB time by one standard deviation resulted in higher values of CRP (3.3%), triglycerides (1.8%), and waist circumference (1.2%). Very small

beneficial associations were observed for insulin (<1%), HOMA-IR (<1%), glucose (<1%), and total cholesterol (1%) when one standard deviation of SB (91 minutes) was reallocated from sleep to SB.

Isotemporal models were repeated after re-categorizing short sleep (<7 hours) and long sleep (>9) hours, and although the percent change of associations increased in some markers, the direction of associations remained consistent.

## **DISCUSSION**

This is one of the first studies to explore the relationship between objectively measured sleep duration and cardiometabolic health in a diverse sample of older women. Our study results are consistent with previous single behavior analyses and meta-analyses demonstrating that objectively measured sleep duration is significantly related to several markers of cardiometabolic health including measures of metabolic function, gluco-regulatory function, and systemic inflammation.<sup>15,17,46,47</sup> Many studies have focused on the relationship between short sleep and glucose metabolism, and the increased risk for diabetes, finding that short sleepers have higher glucose levels and increased risk for diabetes.<sup>11,48,49</sup> Consistent with this previous research, in our analyses, insulin, glucose and HOMA-IR were all significantly related to objective sleep duration. Unlike previous results, in our sample the relationship between sleep duration and glucose was U-shaped with higher values in both short and long sleepers. Further, in our analysis the relationship between sleep and cardiometabolic outcomes appeared to differ across different markers, with a linear relationship for some markers and a u-shaped relationship with CRP, glucose, waist circumference, and RRS. In our study, the U-shape relationship between sleep duration and RRS, suggests that sleep duration, both short and long, is related to higher 10-year estimated CVD risk. The individual cardiometabolic marker results, as well as the RRS results,

align with previous research suggesting there may be different pathways through which short and long sleep duration may be related to increased CVD risk for older women.<sup>46</sup> These findings contribute to the growing research demonstrating that sleep duration, both short and long, is associated with CVD risk.

In order to increase or decrease sleep durations to improve cardiometabolic health, time would need to be reallocated to or from another behavior in the 24-hour day. While growing evidence suggests that sleep duration should be increased in short sleepers or decreased in long sleepers, it is not clear what shift in daytime activity would provide benefit. Isotemporal modeling techniques allow for the exploration of the associated change in cardiometabolic risk of reallocating time spent sleeping when it is shifted to or from LIPA, MVPA, or SB.<sup>28,29</sup> Our study results support increasing sleep duration in short sleepers and decreasing sleep duration in long sleepers, however, these results were dependent on how the 24-hour time was reallocated. The results of our isotemporal analysis are consistent with a previous isotemporal modeling analysis conducted by Buman et al. that examined cardiometabolic risks associated with reallocation of time spent in self-reported sleep, and objectively measured SB and PA among an NHANES sample of 2,185 adults (mean age 46.6).<sup>29</sup> Consistent with the results of Buman et al, our results show that in long sleepers when time was reallocated from sleep to MVPA it was associated with favorable values across all of the cardiometabolic makers. In our analysis, a similar pattern was observed for reallocating time from sleep to LIPA, a result that was not observed in the NHANES sample, and is particularly meaningful in our sample of older women. For our sample of older women, achieving shifts to LIPA may be more feasible than shifts to MVPA. Further, when time was reallocated from SB to sleep in short sleepers it had beneficial associations with several of the cardiometabolic markers, including changes to CRP, waist

circumference and RRS. Building upon the results of the NHANES study, our study used an objective assessment of sleep duration; measured using accelerometry with an average sleep duration calculated from 2-5 nights of sleep and focused on reallocation of time to sleep in short sleepers and from sleep in long sleepers. In contrast, the NHANES study assessed sleep duration with one item on a questionnaire. Our study results provide support for sleep extension interventions in short sleepers, but suggest that how time is reallocated impacts cardiometabolic health. These findings have promising value for translation in clinical practice, but require testing in randomized controlled trials. In cognitive behavior therapy interventions (CBTI), individuals with poor sleep are encouraged to stay out of bed, but keep activity light. Our results suggest that interventions targeting sleep extension, and improved sleep should consider providing recommendations that are both achievable and provide the most cardiometabolic benefits. For short sleepers, replacing SB time in the evening with sleep may be an achievable target with cardiometabolic benefits, or for long sleepers reducing SB time in bed and increasing LIPA throughout the day may provide benefits.

While our study results suggest benefits for increasing or decreasing sleep duration overall, results suggest that replacing MVPA or LIPA with sleep in short sleepers and replacing sleep duration with SB in longer sleepers are shifts in 24-hour time that are not likely to reduce cardiometabolic risk. This finding suggests, that it important to consider the distribution of time throughout the 24-hour day, and the impact of interventions on all 24-hour activity when designing cardiovascular lifestyle interventions to decrease cardiometabolic risk. When developing intervention strategies, it is worthwhile to consider time spent in other activities, regardless of the behavioral target of the intervention. For example, our study results suggest that in both short and long sleepers, sedentary behavior has a detrimental association with markers of

cardiometabolic health and therefore, sleep duration may be an achievable and beneficial replacement activity target for interventions targeting SB reduction.

When using isothermal modeling techniques, and when designing behavior change interventions, the feasibility of behavior change targets is important. One standard deviation change in MVPA, LIPA, and SB is a magnitude of change that may not be realistic for all women in the sample. For example, in our analysis, benefits for MVPA were observed with a 33 minute increase in MVPA, which may not be feasible change for older women when we consider the number of older adults meeting PA guidelines. Further a 90 minute increase in sleep duration of short sleepers may also not be realistic. Previous sleep extension studies in healthy young adults have observed an increase in self-reported sleep duration of approximately 60 minutes.<sup>24,50</sup> The isothermal modeling approach can show us where a benefit can be expected to occur under an ideal shift in time, but the associated magnitude of change is often not realistic. Only randomized control intervention trials can inform what change in cardiometabolic markers we can truly affect with a change in behavior.

A primary strength of our study was the use of accelerometers to measure objectively 24-hour activity. The OPACH study employed hip accelerometers, the gold standard for assessment of daytime PA; however, wrist placement is considered preferable for assessment of sleep.<sup>35,51</sup> Hip worn accelerometers provide a more accurate assessment of SB and sleep duration than self-reported measures.<sup>52-54</sup> Additionally, we employed thoughtful data processing steps to ensure the accuracy of our behavior classification. The in-bed sleep period was defined using participant sleep logs and visual coding, to ensure further the accuracy of the in-bed period. Older women have lower levels of activity throughout the day, which may lead algorithms to misclassify SB as sleep. The visual inspection of in-bed time not only provided more accurate

estimates of sleep duration, but also more accurate estimates of SB, by capturing in-bed sedentary time. In-bed sedentary time is often omitted when SB data processing protocols remove in-bed time from their analyses. Distinguishing between sleep and in-bed sedentary time is important as lying in bed in bed awake does not have the same benefits as sleeping.

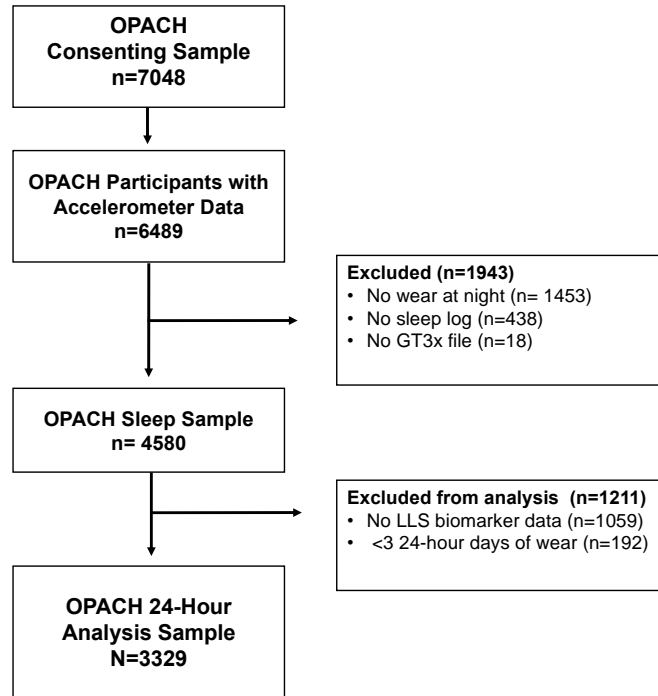
Our study population includes only post-menopausal older women from the unique WHI sample, and therefore may not be generalizable to men or other age groups. However, the study population included larger numbers of older African American and Hispanic women than previous studies that have assessed the relationship between sleep duration and cardiometabolic health. Further, this study is cross-sectional, limiting our ability to make causal inferences about the reallocation of time spent in one behavior to another. Our study findings do not represent actual activity replacement, but the estimated results of modeling shifts in population-level data. Lastly, our study would have benefited from objective measurement of postural change to estimate SB and the time that older woman spend in bed not sleeping.

Cardiovascular interventions for older women should continue to target increasing LIPA and MVPA and reducing SB, but also consider sleep duration as a lifestyle risk factor worth targeting for cardiometabolic risk reduction. Designing sleep duration interventions or including sleep behavioral targets in existing lifestyle interventions, may provide a feasible target for older women who are short or long sleepers. Future research should explore the interrelationships of activity throughout the 24-hour day, including using a compositional approach to statistical analyses. Moreover, future cardiovascular lifestyle interventions should examine further the possibility of multiple behavior targets, including more specific activity replacement targets, and tailoring intervention targets for feasibility.



## **ACKNOWLEDGEMENTS**

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**Figure 1.1:** OPACH study participant flow diagram

**Table 1.1:** Participant characteristics for the OPACH cohort by sleep duration categories

	Full Sample N=3329	Short Sleepers <8 hours n=1486	Long Sleepers ≥8 hours n=1843	P- value
	Mean ± SD N (%)	Mean ± SD N (%)	Mean ± SD N (%)	
<b>Age, years</b>	78.9 ± 6.7	78.0 ± 6.6	79.7 ± 6.7	<.001
63-69	330 (9.9)	179 (12.0)	151 (8.2)	<.001
70-79	1275 (38.3)	623 (42.0)	652 (35.4)	
80-89	1576 (47.3)	635 (42.7)	941(51.1)	
≥90	148 (4.4)	49 (3.3)	99 (5.4)	
<b>Race-ethnicity</b>				<.001
White	1782 (53.5)	734 (49.4)	1048 (56.9)	
Black	991 (29.8)	482 (32.4)	509 (27.6)	
Hispanic	556 (16.7)	270 (18.2)	286 (15.5)	
<b>Education</b>				0.71
High school or less	686 (20.6)	310 (20.9)	376 (20.5)	
Some college	1285 (38.6)	563 (38.0)	722 (39.4)	
College graduate	1340 (40.3)	607 (41.0)	733 (40.0)	
<b>Current smoker</b>	78 (2.3)	43 (2.9)	35 (1.9)	0.08
<b>Sleep Disturbance Score</b>	6.3 ± 4.5	6.0 ± 4.4	6.5 ± 4.5	<0.01
<b>BMI, kg/m<sup>2</sup></b>	27.8 ± 5.7	28.2 ± 5.8	27.6 ± 5.5	<0.01
≥30 (obese)	976 (29.3)	460 (31.2)	516 (28.2)	0.12
<b>Comorbidity Index</b>				
≥2 comorbidities	518 (15.6)	202 (13.6)	316 (17.1)	<.01
<b>Self-report Health</b>				
At least good	2792 (83.9)	1277 (92.9)	1515 (89.0)	<.001

BMI, body mass index

Note: Numbers do not sum to total due to missing data

**Table 1.2:** Summary of 24-hour time spent in each daily activity by sleep category

	<i>Short sleepers (&lt;8 hours)</i>	<i>Long sleepers (≥8 hours)</i>
	<i>Mean (SD)</i>	<i>Mean (SD)</i>
<b>Wear time (mins/day)</b>	1370.32 (44.2)	1388.35 (43.1)
<b>MVPA (mins/day)</b>	55.69 (37.2)	44.15 (31.2)
<b>LIPA (mins/day)</b>	298.76 (77.2)	257.85 (71.1)
<b>SB (mins/day)</b>	593.66 (93.9)	541.91 (84.6)
<b>Sleep (mins/day)</b>	428.32 (42.4)	539.74 (50.2)

MVPA: moderate to vigorous physical activity

LIPA: light physical activity

SB: sedentary behavior

**Table 1.3:** Single variable models<sup>1</sup> for sleep duration and estimated cardiometabolic markers

	<i>6 hours</i>	<i>8 hours</i>	<i>10 hours</i>		<i>B<sup>++</sup></i>	<i>SE</i>	<i>p value</i>
<b>Insulin (mmol/L)</b>							
	59.39	63.22	70.88	Linear term	0.952	0.021	<b>&lt;0.001</b>
				Quadratic term	--	--	--
<b>C-Reactive Protein (mg/L)</b>							
	1.77	1.78	2.04	Linear term	-3.903	0.242	0.11
				Quadratic term	0.005	<0.001	<b>0.05</b>
<b>HOMA-IR</b>							
	1.41	1.48	1.57	Linear term	0.447	0.010	<b>&lt;0.001</b>
				Quadratic term	--	--	--
<b>Glucose (mg/dL)</b>							
	98.28	97.23	100.11	Linear term	-1.226	0.063	<b>&lt;0.05</b>
				Quadratic term	0.001	<0.001	<b>&lt;0.05</b>
<b>HDL cholesterol (mmol/L)</b>							
	61.20	60.88	60.57	Linear term	- 0.026	0.004	0.53
				Quadratic term	--	--	--
<b>Total cholesterol (mmol/L)</b>							
	194.01	197.13	200.26	Linear term	0.257	0.011	<b>&lt;0.05</b>
				Quadratic term	--	--	--
<b>Triglycerides (mg/dL)</b>							
	89.79	96.60	103.95	Linear term	0.006	0.012	<b>&lt;0.001</b>
				Quadratic term	--	--	--
<b>Systolic Blood Pressure</b>							
	125.17	125.38	125.58	Linear term	0.017	0.004	0.67
				Quadratic term	--	--	--
<b>Waist Circumference (cm)</b>							
	90.20	88.91	89.34	Linear term	-0.608	0.031	<b>&lt;0.05</b>
				Quadratic term	0.001	<0.001	<b>0.05</b>
<b>BMI (kg/m<sup>2</sup>)</b>							
	27.9	27.78	27.65	Linear term	-0.011	0.001	0.46
				Quadratic term	--	--	--
<b>Reynolds Risk Score (%)<sup>2</sup></b>							
	12.02	11.68	14.69	Linear term	-1.011	0.024	<b>&lt;0.001</b>
				Quadratic term	0.001	<0.001	<b>&lt;0.001</b>

<sup>1</sup> Models adjusted for wear time, age, race/ethnicity, education, sleep disturbances, self-rated health, smoking status, and comorbid conditions

<sup>2</sup> Reynolds Risk Model did not include age in adjustments – age is included in Reynolds Risk Score calculation

++Beta coefficients are log transformed and reflect associations for 10 mins of sleep duration

**Table 1.4:** Single variable models<sup>1</sup> for MVPA, LIPA, and SB and cardiometabolic markers

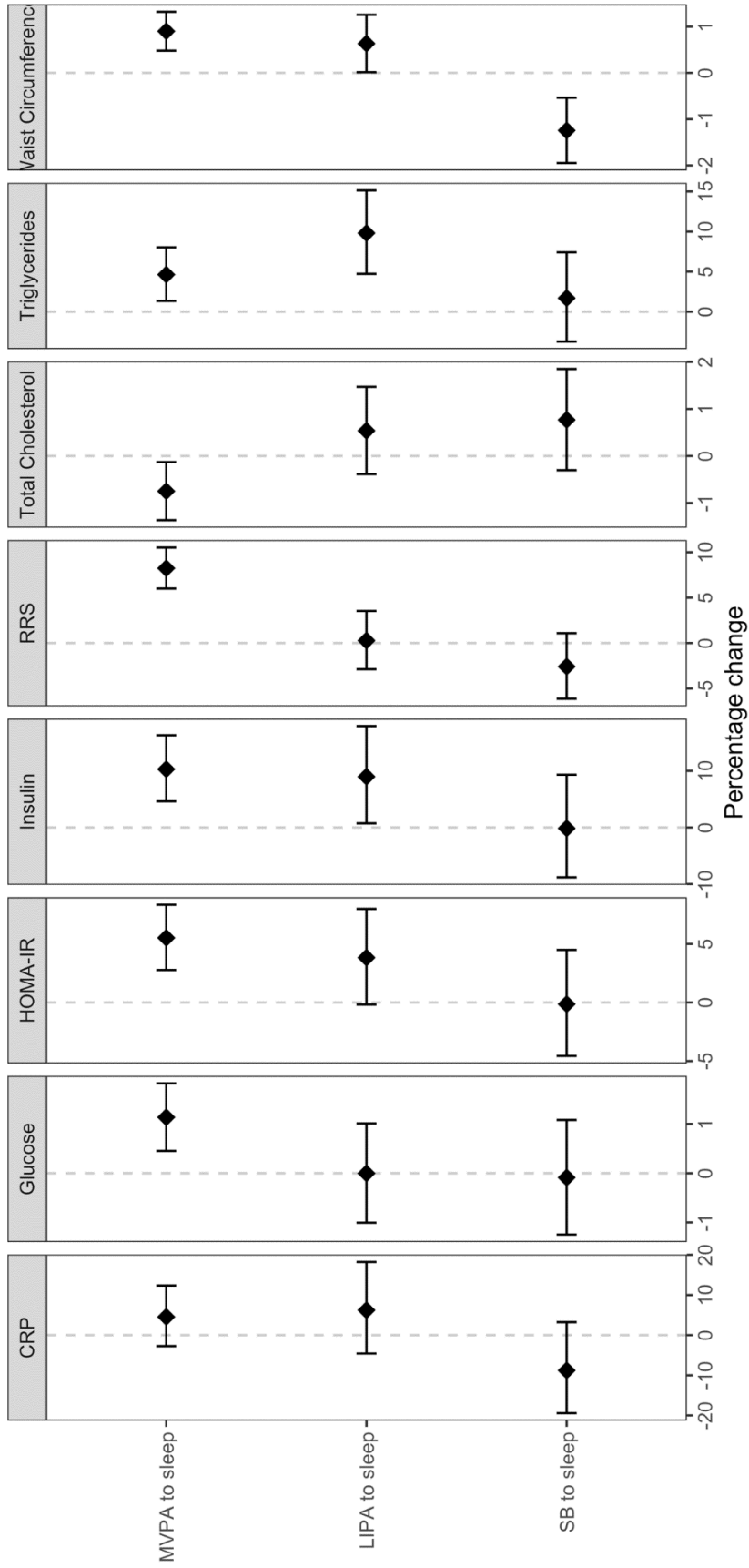
		<i>B</i> <sup>++</sup>	<i>SE</i>	<i>p</i> value
<b>Insulin (mmol/L)</b>				
	MVPA	-4.239	0.044	<0.001
	LIPA	-1.855	0.019	<0.001
	SB	1.061	0.015	<0.001
<b>C-Reactive Protein (mg/L)</b>				
	MVPA	-4.080	0.061	<0.001
	LIPA	-2.496	0.027	<0.001
	SB	1.611	0.021	<0.001
<b>HOMA-IR</b>				
	MVPA	-2.185	0.022	<0.001
	LIPA	-0.907	0.010	<0.001
	SB	0.544	0.008	<0.001
<b>Glucose (mg/dL)</b>				
	MVPA	-0.985	0.016	<0.001
	LIPA	-0.274	0.007	<0.001
	SB	0.217	0.006	<0.001
<b>HDL cholesterol (mmol/L)</b>				
	MVPA	0.777	0.009	<0.001
	LIPA	0.408	0.004	<0.001
	SB	-0.328	0.003	<0.001
<b>Total cholesterol (mmol/L)</b>				
	MVPA	1.317	0.023	<0.001
	LIPA	0.210	0.010	<0.05
	SB	-0.444	0.008	<0.001
<b>Triglycerides (mg/dL)</b>				
	MVPA	-1.835	0.026	<0.001
	LIPA	-1.287	0.011	<0.001
	SB	0.671	0.009	<0.001
<b>Systolic Blood Pressure</b>				
	MVPA	-0.276	0.008	0.001
	LIPA	-0.155	0.004	<0.001
	SB	0.121	0.003	<0.001
<b>Waist Circumference (cm)</b>				
	MVPA	-1.155	0.008	<0.001
	LIPA	-0.556	0.003	<0.001
	SB	0.480	0.003	<0.001
<b>BMI (kg/m<sup>2</sup>)</b>				
	MVPA	-0.382	0.003	<0.001
	LIPA	-0.222	0.001	<0.001
	SB	0.183	0.001	<0.001
<b>Reynolds Risk Score (%)<sup>2</sup></b>				
	MVPA	-0.838	0.006	<0.001
	LIPA	-0.300	0.003	<0.001
	SB	0.216	0.002	<0.001

<sup>1</sup> Models adjusted for wear time, age, race/ethnicity, education, sleep disturbances, self-rated health, smoking status, and comorbid conditions

<sup>2</sup> Reynolds Risk Model did not include age in adjustments – age is included in Reynolds Risk Score calculation

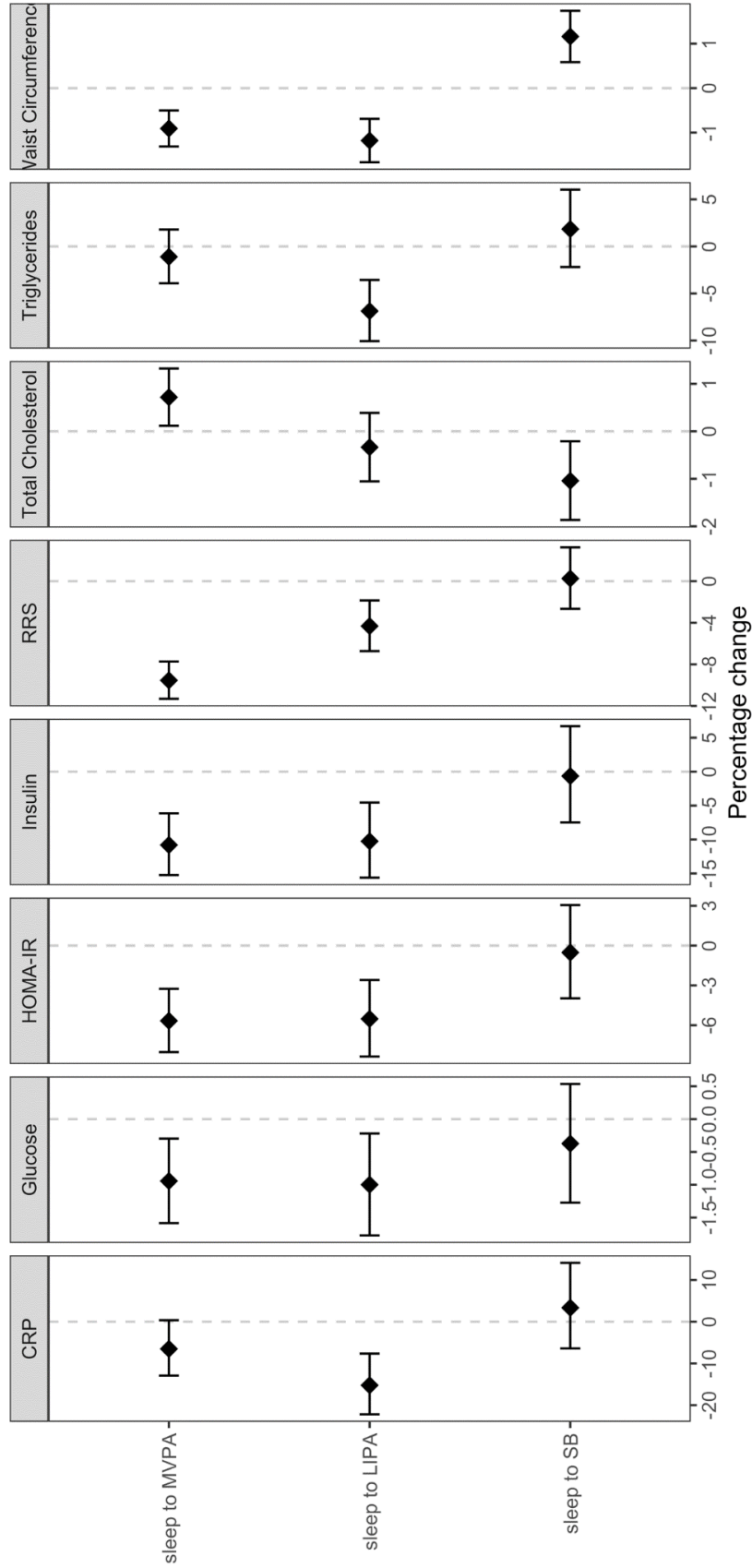
++Beta coefficients reflect associations for 10 mins of activity

### Short Sleep: Reallocation of 1 SD of Activity to Sleep and Percent Change to Cardiometabolic Markers



**Figure 1.2:** Short sleep: Associated changes of reallocation of 1 SD of activity to sleep. MVPA: moderate to vigorous physical activity. LIPA: light physical activity. SB: sedentary behavior

Long Sleep: Reallocation of 1 SD of Activity from Sleep and Percent Change to Cardiometabolic Markers



**Figure 1.3:** Long sleep: Associated changes of reallocation of 1 SD of activity from sleep. MVPA: moderate to vigorous physical activity. LIPA: light physical activity. SB: sedentary behavior.

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## CHAPTER 2

### **Association between Accelerometer-Measured Sleep Duration and Clinical Cardiovascular Risk Factor Scores in Older Women**

#### **ABSTRACT**

**Background:** Emerging evidence suggests that sleep duration, both short and long, is a potential modifiable lifestyle factor associated with cardiovascular disease (CVD). However, research on sleep duration and CVD risk is limited by use of self-report sleep measures, homogeneous populations, and studies on individual CVD risk factors. As women age their risk of CVD increases, as does their risk for sleep disturbances. Based on this framework, we sought to test the hypothesis that accelerometer-measured sleep duration would be related to estimated CVD risk among a diverse group of aging women.

**Methods:** Cross-sectional data were analyzed in 3369 racial/ethnically diverse older women (mean age 78.9 years; 53.3% white, 29.9% black, 16.8% Hispanic), from the Objective Physical Activity and Cardiovascular Health Study, an ancillary study to the Women's Health Initiative. Women wore ActiGraph GT3X+ accelerometers on the hip for 24 hours per day and completed a daily sleep log over a 7-day period. A composite of 10-year estimated CVD risk, the Reynolds Risk Score (RRS), was computed using age, systolic blood pressure, high-sensitivity C-reactive protein (CRP), total and HDL cholesterol, diabetes mellitus status, smoking status, and family history of premature myocardial infarction. Average nightly sleep duration was derived from accelerometer data. A series of progressively adjusted linear regression models investigated the strength of the association between sleep duration and RRS.

**Results:** Results suggested a U-shaped relationship between sleep duration and RRS, such that both short and long sleep are associated with higher RRS. The association remained

significant after adjustments for race/ethnicity, education, lifestyle factors, BMI, self-reported sleep disturbances, sleep medications, and comorbidities.

**Conclusions:** In older women, actigraphy-ascertained sleep duration was associated with 10-year estimated CVD risk. Both short and long sleep were related to higher RRS in multivariable adjusted analyses. This study, based on accelerometer-measured rather than self-reported sleep, supports sleep duration as a modifiable risk factor for CVD in older women.

## INTRODUCTION

Cardiovascular disease (CVD) poses a serious risk to the growing aging population of women in the United States.<sup>1</sup> According to the American Heart Association, more than one in three US women currently has some form of CVD.<sup>2</sup> Women over the age of 80 years have a higher incidence of CVD events than their male counterparts.<sup>2</sup> The American Heart Association estimates that approximately 90% of women in the United States are currently living with one or more risk factors for developing CVD.<sup>2</sup> There are a number of modifiable risk factors for CVD including obesity, physical inactivity, elevated total cholesterol, reduced HDL cholesterol, diabetes, smoking, hypertension, and systemic inflammation as measured by elevated high-sensitivity C-reactive protein (CRP).<sup>3</sup> Cardiovascular prevention strategies for women focus on the promotion of daily physical activity and a well-balanced diet.<sup>2</sup> The continuing high burden of clinical CVD and its risk factors among women suggest that enhancing current prevention strategies could be warranted to achieve better control of CVD at the population level.

Emerging evidence suggests that sleep duration, both short (<7 hours) and long (>9 hours), is a potential lifestyle risk factor for CVD.<sup>4</sup> A number of cross-sectional and prospective observational studies demonstrate that self-reported short sleep (<7 hours) is a predictor of incident cardiometabolic conditions such as type 2 diabetes, hypertension, and obesity.<sup>5-10</sup> A meta-analysis of prospective studies examining the relationship between self-reported sleep duration and coronary heart disease (CHD), found that among a total sample of 249,324 adults, short sleepers (those sleeping less than 7 hours) had an approximate 50% increase in risk of developing or dying from CHD when compared with normal sleepers (those sleeping 7-8 hours).<sup>11</sup> Additionally, those who reported long sleep durations (more than 8 hours) experienced a 38% increased risk of CHD when compared to normal sleepers.<sup>11</sup>

Previous evidence of the relationship between sleep duration and CVD risk is not without limitations. The majority of published studies have relied on self-reported sleep duration from 1 or 2 survey items, and have focused on study samples primarily consisting of middle-aged non-Hispanic white adults.<sup>12</sup> While CVD incidence is higher in older women, and African American and Non-white Hispanic populations<sup>2</sup>, most published studies on sleep and CVD risk have not adequately included women with broad representation from these age and race-ethnic groups.<sup>4,13</sup> Additionally, evidence has demonstrated that sleep duration and quality differs across age groups and racial/ethnic groups.<sup>14,15</sup> According to the American Heart Association Scientific Statement on the relationship between sleep duration and CVD, inclusion of these understudied populations, including aging women and African American and Non-white Hispanic women, and the objective assessment of sleep, should be high priorities for future research.<sup>4</sup> Further, previous studies have primarily examined the relationship between sleep duration and individual CVD risk factors such as systolic blood pressure and BMI, with reviews and meta-analyses compiling data to draw conclusions about overall cardiometabolic risk.<sup>11-13,16</sup> While examining CVD risk factors individually may explain the relationship between sleep and cardiometabolic health at a given point in time, they may not explain the relationship between sleep and risk of future CVD. Further, in the clinical setting, composite risk factor scores are the conventional first-line approach to predict an individual's future CVD risk and to help decide need for further testing (e.g. stress testing, coronary calcium measurements) and initiation of therapeutic intervention.<sup>17</sup>

The objective of this paper is to examine the relationship between accelerometer-measured sleep duration and estimated CVD risk (using the Reynolds Risk Score) in a large racially/ethnically diverse cohort of older women. The Reynolds Risk Score (RRS) is used clinically to predict 10-year risk of CVD.<sup>18</sup> This analysis will test the hypothesis that



accelerometer-measured sleep duration is related to CVD risk among a diverse group of aging women. Results from this analysis could inform the potential utility of including sleep duration in clinical guidelines on CVD prevention.

## **METHODS**

### ***Study Sample***

Women in the study were enrolled for participation in the Objective Physical Activity and Cardiovascular Health (OPACH) study, an ancillary study to the Women's Health Initiative (WHI). From 1993 to 1998, postmenopausal women between the ages of 50 to 79 years were enrolled in the WHI Clinical Trials or the Observational Study from 40 clinical sites throughout the US. Participants in the WHI studies continue to be followed annually for disease events, changes in health status, and death. To be eligible and enrolled in Extension Studies women were required to be alive, willing to be contacted, and willing to provide additional informed consent. The OPACH study aimed to examine prospectively the relationship between accelerometer-measured physical activity and incidence of CVD in older women. Information on the OPACH study objectives, recruitment, and methodology have been previously published.<sup>19</sup> Between 2012-2013, women participating in the WHI Long Life Study (LLS) completed in home health assessments to assess factors associated with healthy aging and cardiovascular health. In home data collection included fasting blood draws, personal health and lifestyle questionnaires, anthropometric measurements, and blood pressure and pulse assessments. A subset of LLS participants (N=7048) agreed to participate in the OPACH study, received GT3x accelerometer devices, and were asked to wear them on their waist for 24 hours per day over a 7-day period. Additionally, participants were asked to complete sleep logs and report their in-bed time and out-of-bed time for the 7-day accelerometer wear period. Of the 7048 consented participants, 6,489

women returned their devices and provided at least one day of valid accelerometer data ( $\geq 10$  hours/day wear time); 4,580 of these women had valid night wear and completed sleep logs. Of these, 3,369 met eligibility criteria for inclusion in this analysis, including completion of at least 3 nights of valid accelerometer data, a completed sleep log that overlapped with accelerometer nights, and information on fasting blood lipids (Figure 2.1). In consideration of night to night sleep variation, previous sleep studies have demonstrated that one night of accelerometer wear is not sufficient to assess regular sleep habits.<sup>20</sup> Additionally, previous cohort studies examining cardiovascular health have defined valid wear as three nights.<sup>21</sup>

### ***Accelerometer-Measured Sleep Duration***

Sleep duration was assessed with the hip-worn triaxial accelerometer (Actigraph GT3X+; Pensacola, FL). Participants were asked to wear the accelerometer device secured to their hip with a belt, 24 hours a day for 7 consecutive days, except for time spent bathing or swimming. Data were recorded in 1-second epochs collected at a frequency of 30 Hertz. In addition, participants were asked to complete a daily sleep log recording time in bed and time out of bed. Although wrist-worn accelerometer devices are more standard for sleep assessment, hip-worn accelerometers are the norm for physical activity studies like OPACH.<sup>22,23</sup> Outside of the lab setting, the use of hip accelerometers to assess sleep duration has been shown to be valid for assessment of total sleep duration against the gold standard polysomnography.<sup>23,24</sup> Accelerometer estimated sleep duration is considered more accurate than self-reported sleep duration or sleep logs alone,<sup>25</sup> especially in older adult populations where cognitive issues may be present.<sup>26</sup>

After the device was returned, raw data were processed using ActiLife version 6.11 software. Raw data were condensed to 60 second AGD files with the low frequency extension

filter. AGD files were scored for sleep variables using a standard protocol. A trained member of the research team identified the primary sleep window using the participant sleep logs and visual review of the data for each night the participant wore the device. This procedure draws from a protocol shown previously to have high interrater reliability.<sup>27</sup> The validated Cole-Kripke algorithm<sup>28</sup> classified the sleep interval on a minute by minute basis as sleep or wake and estimates of nightly sleep duration were derived as the total amount of time classified as sleep (minutes/night) during the primary sleep period. Mean sleep duration was calculated across the available days of scored sleep (ranging from 3-7) to create an average nightly sleep duration variable. Previous studies have examined short sleep duration as <6 or <7 hours of sleep/night and long sleep duration as >9 or >10 hours of sleep/night, due to self-reported assessment response categories. Because a clear and well-established definition of short or long sleep duration currently does not exist, we conducted our analysis retaining sleep duration as a continuous variable.

### ***10 Year Estimated CVD Risk: Reynolds Risk Score***

The Reynolds Risk Score (RRS) for 10-year predicted CVD risk was calculated as a composite variable which has demonstrated accuracy in the prediction of future CVD occurrence in women, as described elsewhere.<sup>18</sup> RRS is calculated using age, systolic blood pressure (SBP), CRP, total and HDL cholesterol, diabetes mellitus status, smoking status, and family history of premature myocardial infarction. In a previous study conducted in the WHI cohort the RRS demonstrated good validity in the prediction of actual CVD events, and performed better in the validation cohort of older woman than the Framingham ATP-III Score.<sup>29</sup> Hemoglobin A1c was not assessed in the OPACH study; therefore, this variable was not included in the RRS

calculation (for those who report a history of diabetes diagnosis as specified in the RRS scoring protocol).

At the LLS home visit, blood samples were obtained. Participants were instructed to fast for 12 hours prior to the blood draw. Samples were centrifuged within 2 hours of blood draw, and shipped overnight priority mail to the Fred Hutchinson Cancer Research Center Specimen Processing Laboratory (Seattle, Washington). An aliquot for each participant was sent from the WHI Biorepository to the University of Minnesota Fairview ARDL Laboratory for CVD biomarker testing. The biomarkers required in the RRS were obtained from these test results. Resting blood pressure (BP) was measured after a 5-minute rest period using an aneroid sphygmomanometer and cuff size based on measured arm circumference. The average of two BP readings was recorded. Diabetes mellitus status, smoking status, and family history of premature myocardial infarction were assessed using the LLS questionnaire.

### *Covariates*

LLS and WHI questionnaires ascertained demographic information, education, alcohol intake, smoking, self-reported physical functioning, self-rated health, self-reported sleep disturbances, sleep medication use, and history of chronic conditions.

Education was categorized into 3 levels: high school or less, some college, college graduate or more. Alcohol intake was measured with 1-item assessing the frequency of consuming gram standardized alcoholic drinks the past three months. Response options ranged on a 5-point scale from “never” to “everyday”. Physical functioning was assessed with the RAND 36-item health survey.<sup>30</sup> A score was calculated ranging from 0-100, with higher values signifying better physical functioning. Self-rated health was assessed with 1-item from the WHI lifestyle questionnaire asking participants “In general would you say your health is...”. Response

options ranged on a 5-point scale from “excellent” to “poor”. Depression was assessed with the WHI Depression Scale,<sup>31</sup> a short form adaptation of the CES-D scale. Scale scores ranged from 0-1 with higher values indicating a higher presence of depressive symptoms. Sleep disturbances were assessed with the WHI Insomnia Rating Scale (WHIIRS).<sup>32</sup> A scale score is calculated from the five item scores (0-4) to create a global sleep disturbance score ranging from 0-20. A higher WHIIRS score is reflective of greater presence of sleep disturbances and has been shown to be predictive of CVD.<sup>33</sup> The use of sleep medications was assessed with 1-item assessing in the last 4 months, how many times per week a participant used sleep medications. Response options ranged from “None in the past 4 weeks” to “5 or more times per week”. A comorbidity index variable was created using the self-report of existing chronic conditions collected in the baseline survey. The index included self-report of history of chronic obstructive pulmonary disease (COPD), history of osteoarthritis, history of cerebrovascular disease, history of cancer, history of cognitive impairment, and history of hip fractures. The number of conditions was summed to create a comorbidity index score (0-6).

Height (cm) and weight (kg) were measured using a portable scale and stadiometer. Participants Body Mass Index (BMI; kg/m<sup>2</sup>) was calculated with the height and weight obtained at the LLS study visit. Total daily physical activity (minutes/day) were measured using the GT3x accelerometer.

### ***Statistical Analysis***

Descriptive analyses tested for differences in demographic, medical and behavioral factors in the sample across four categories of sleep duration using One-Way ANOVAs for continuous variables and Chi-square tests for proportions.

Progressively adjusted linear regression models and marginal means plots were used to evaluate the relationship between average nightly sleep duration and RRS. The first model was minimally adjusted for race/ethnicity and education. Because age is included as a component of the RRS, it was not adjusted for in the regression models. The second series of adjustments included alcohol intake, total minutes of physical activity, sleep disturbance score, and sleep medications. Further adjusted models included BMI, physical functioning, comorbidity index score, depression, and self-rated health, all of which could potentially mediate an association between sleep duration and estimated CVD risk.

The literature suggests both short and long sleep durations are related to increased risk for CVD. Therefore, we tested if the relationship between sleep and RRS was non-linear by including a quadratic term for sleep duration in this series of models.

All analyses were performed using R statistical software version 3.1.1.<sup>34</sup>

## **RESULTS**

In this cross-sectional analysis, we excluded the participants who had fewer than 3 nights of accelerometry data (n=152) or were missing biomarker data (n=1059), resulting in a final analytic sample of 3,369 women. There were statistically significant differences in the age and in the proportion of the race/ethnicity groups between the subsample of women with 3 valid nights of accelerometer than women in the entire OPACH study who returned at least one day of accelerometer data (N=6489); however, there were no significant differences based on hours of self-reported sleep duration. The 3369 women included in the sleep sample were slightly older (mean age: 78.9 vs 78.5 years,  $p<.01$ ), and the sample had a larger proportion of white women (53% vs 45%), and a smaller proportion of African American women (30% vs 38%,  $p<.001$ ) than the original OPACH sample.

The analytic sample had an average nightly sleep duration of 8.16 hours (SD: 71.4). There were 517 (15.3%) women who had an accelerometer-measured sleep duration of less than 7 hours, 975 (29.0%) between 7 and 8 hours, 1149 (34.1%) between 8 and 9 hours, and 728 (21.6%) greater than 9 hours. Characteristics of the study sample are presented for descriptive purposes according to sleep duration quartiles in Table 2.1.

The average age of women in the sample was 78.9 years (SD:6.7), and 53.3% of women were white, 29.9% black, and 16.8% Hispanic. Over 80% of participants had at least some college level education. Over 60% of the sample reported drinking some alcohol and only 2.3% were currently smokers. The average sleep disturbance score of the sample was 6.3 out of 20 (SD: 4.5). Over 18% of the sample reported presence of 2 or more comorbidities, but 83.9% reported at least good general health. The mean BMI among all women was 27.9 kg/m<sup>2</sup>, with almost 1/3 of women in the sample categorized as obese (BMI >30 kg/m<sup>2</sup>), and 19.4% of the sample had a history of diagnosed or treated diabetes mellitus.

Women who slept less than 7 hours were, on average, significantly younger and more likely to be African American or Hispanic as compared to women with longer sleep durations. Education level did not differ across the sleep categories. The short sleepers (<7 hours) were less likely to be regular drinkers, had a lower sleep disturbance score, and higher levels of daily physical activity than women in the other sleep categories. Short sleepers were also more likely to be current smokers and have a diabetes diagnosis compared to non-short sleepers.

Women in the 7-8 hour and 8-9 hour categories were more likely to be white women than African American or Hispanic. Drinking more than 5 alcoholic drinks per week was more commonly reported by women who slept in the 7-8 and 8-9 hour categories than in the other two categories.

Sleep disturbance scores, reported sleep medication use, depression, and the proportion of the sample with more than 2 comorbidities was highest in the >9 hours of sleep category. Additionally, physical functioning scores, total daily physical activity, and the proportion of the sample reporting good to excellent self-rated health were lowest among women in the >9 hours of sleep category.

Differences in the individual components of the Reynolds risk Score were examined across sleep duration categories and no significant differences were observed in the individual risk factors between categories, except for smoking status, which was higher among short sleepers. Of note, women in both the <7 hours of sleep category and the >9 hours of sleep category had a higher prevalence of diabetes than women in the 7-8 and 8-9 hours of sleep categories.

After adjustment for race/ethnicity and education, both sleep duration and the quadratic sleep duration term were significantly related to RRS (Figure 2.2; sleep duration:  $B: -0.11$   $p < 0.001$ , sleep duration<sup>2</sup>  $B: < 0.00$   $p < 0.001$ ). Figure 2.2 displays this minimally adjusted relationship between accelerometer-measured sleep duration and RRS. The relationship appears to be U-shaped, with both short (<400 minutes/night; <6.5 hours/night) and long (>500 minutes/night; >8 hours/night) sleep associated with higher RRS as compared to the middle of the sleep duration distribution. In the series of progressively adjusted models the quadratic sleep duration term was significantly associated with RRS after adjustments for lifestyle factors including alcohol intake, physical activity, sleep disturbances, and sleep medications (Figure 2.3; sleep duration<sup>2</sup>  $B: < 0.00$   $p < 0.001$ ). Results were similar after further adjustment for BMI, physical functioning, comorbidity index score, depression, and self-rated health. In this final



model sleep duration remained significantly related to RRS after adjustment (Figure 2.4; sleep duration<sup>2</sup> B: <0.00 p<0.01).

The series of progressively adjusted models are illustrated in Figures 2.2-2.4 to show the u-shaped relationship between sleep duration and estimated 10-year CVD risk. While the coefficients for the quadratic sleep duration variables in the series of progressive adjustments do not reflect attenuation, the plots show the shape of the curve changing after adjustment. Despite the change in the shape of the plots, the relationship between sleep duration and RRS remains significant, with both short and long sleep associated with higher RRS. Table 2.2 provides the estimated RRS from the series of models for each hour per night of sleep. The table provides a quantification of what is shown in the figures, with both short, and long sleep durations related to higher RRS. The relationship between long sleep duration (>10 hours) and RRS is very clearly attenuated after the progressive adjustment. Further, the relationship between shorter sleep duration (<6 hours) and RRS appears to become stronger after the series of adjustments.

Although age is a risk factor for CVD and is related to sleep, our main analysis does not adjust for age, as it is a component of the RRS. Adjustment for a variable that is included in the composite RRS could lead to over adjustment of the models. We did, however, complete a sensitivity analysis to further explore if the relationship between RRS and sleep was consistent in older and younger women by stratifying our final model by age. The relationship between sleep duration and RRS was not significant in younger women (<80 years; sleep duration: B: -0.025 p=0.25, sleep duration<sup>2</sup> B: <0.00 p=0.29), but remained significant in older women (>80 years; sleep duration: B: -0.083 p<0.05, sleep duration<sup>2</sup> B: <0.00 p<0.05).

## DISCUSSION

This cross-sectional study of older women is one of the largest studies published to provide additional evidence that sleep duration, measured with accelerometry, is associated with a measure of CVD risk in women. We observed significant associations of sleep duration with 10-year estimated CVD risk, measured by the composite Reynolds Risk Score, which persisted after progressively adjusting for demographics, known lifestyle CVD risk factors, and other possible confounders including sleep medication use. The nature of the relationship between sleep duration and CVD risk remains a topic of investigation and our study suggest that sleep duration is non-linearly related with estimated CVD risk among older women in the community. Both shorter- and longer sleep duration was associated with higher 10-year CVD risks estimated by the RRS. Prospective studies that relate objectively measured sleep duration with the incidence of CVD events are need to clarify the cross-sectional findings of the present study.

Our analysis builds upon previous evidence demonstrating a relationship between sleep duration and CVD risk. The Sleep Heart Health Study, a community-based sample of 5910 adult men and women over the age of 40 years, assessed sleep duration with a one item self-report. The relative odds of hypertension were 60% (OR 1.60, 95% CI, 1.35-2.04) and 30% (Or 1.30, 95% CI, 1.04-1.62) higher in participants sleeping fewer than 6 hours and more than 9 hours per night, respectively, when compared with those sleeping 7 to 8 hours per night.<sup>35</sup> Consistent with our results, the Sleep Heart Health Study reported a u-shaped relationship between sleep duration and risk of hypertension. The Wisconsin Sleep Cohort Study included 1,024 men and women, mean age of 52.7, whose sleep was evaluated using overnight polysomnography. A U-shaped association between sleep duration and obesity was observed, with individuals who sleep less than and more than 7.5 hours per night having increased likelihood of obesity.<sup>36</sup> In the Chicago

Area Sleep Study on 650 adult men and women, ages 35-64, there was no relationship found between sleep duration measured by actigraphy and cardiometabolic markers including hypertension, diabetes, or obesity.<sup>37</sup> The authors attributed the absence of findings to the longer average sleep duration and an unusual lack of short sleepers in their sample. These results may also be due to the small study sample. We had a larger sample with a greater proportion of both short and long sleepers, which may explain the significant findings of both the linear and quadratic term in our study results. Additionally, we did not focus on assessing a relationship between sleep duration and a single CVD risk factor such as obesity or hypertension, but rather a composite clinical risk factor score, RRS, which takes into account both the number and relative contribution of the individual risk factors in estimating the 10-year risk of a cardiovascular event. In our sample, many of the individual risk factors for CVD, including systolic blood pressure and BMI did not differ significantly across sleep duration quartiles. These results suggest that assessing the relationship between sleep duration and individual CVD risk factors may not sufficiently reflect the increased risk for future CVD events associated with short or long sleep duration.

The average age of women in the OPACH sleep sample was almost 79 years, making this one of the oldest cohorts in which the relationship between accelerometer- measured sleep duration and CVD has been examined. In a previous WHI study among 86,329 older women, ages 50-79 (84% white), the relationship between sleep duration measured by one-item self-report and incident CHD and CVD was examined.<sup>33</sup> In models adjusted for age and race, short (<5 hours) and long (>10 hours) sleep duration was associated with a significantly higher risk of CHD (25% and 43%) and CVD (19% and 37%), however results did not remain significant after further adjustment.<sup>33</sup> Our results are similar to the results of the minimally adjusted models, with

an increase in estimated risk observed in both short and long sleepers. Though the sample of this previous WHI study is similar, our study sample is older (mean age of 78.9 years) and substantially more diverse (only 53.5% white). The oldest women (>80 years) comprised most of the long sleep quartile (>9 hours). Older age may be an additional risk factor for long sleep that has not been sufficiently examined.<sup>38</sup> Further, the results of our sensitivity analysis demonstrate that the relationship between sleep duration and RRS does differ between younger and older women in our cohort. Thus, it appears that sleep might influence CVD risk factors and their integrated effect on predicted risk of a future CVD event differently in older compared with younger women. Additional research is needed to better understand how sleep and age interrelate with propensity for cardiovascular disease.

While the existing literature on the detrimental effects of long sleep are mixed, studies have shown that long sleep durations are associated with increased risk of chronic conditions and increased risk of mortality.<sup>39-42</sup> We add to this literature, demonstrating that accelerometer-measured long sleep duration is related to increased 10-year estimated CVD risk. While we controlled for comorbidities, self-reported sleep disturbances, depression, and other possible confounders that may partially explain this relationship, with cross-sectional data we are not able to examine the potential pathways through which sleep duration is linked to estimated CVD risk. Studies suggest there are several biological pathways through which short sleep is related to cardiometabolic health, including: alterations in glucose metabolism,<sup>43</sup> insulin resistance,<sup>44</sup> appetite regulation,<sup>4</sup> and inflammation.<sup>45</sup> The mechanisms between long sleep duration and cardiometabolic health are not as clear, however after controlling for possible confounders (e.g. physical activity, depression, sleep medications) studies have shown that long sleep durations are also related to markers of gluco-regulatory function and systemic inflammation.<sup>46,47</sup> Similar to

previous studies, we tried to adequately control for factors related to health and sleep duration, including depression, socio-economic status, physical functioning, physical activity, and sleep medications. After these adjustments the relationship between short and long sleep duration and estimated CVD risk remained significant.

The primary strength of our study was the use of actigraphy to measure sleep duration, a more accurate assessment of sleep duration than a self-reported measure. Previous cohort studies have relied upon 1- or 2-item self-reported measures of sleep duration to examine how sleep duration may be related to CVD risk. Validity studies have shown that individuals are likely to report sleep times that align with what is perceived as acceptable and often are over-reporting their sleep time.<sup>48,49</sup> While evidence suggests the prevalence of self-reported poor sleep and short sleep varies across racial/ethnic groups,<sup>50</sup> less is known about how reporting bias may vary across these groups. Our study employed hip accelerometers, which are less commonly used for sleep assessment, but have been validated for total sleep duration.<sup>51,52</sup> Additionally, we employed additional data processing and quality control steps to ensure the accuracy of the data. The in-bed sleep period was defined using participant sleep logs and visual coding protocol by a team of trained coders, to ensure further the accuracy of the in-bed and out-of-bed participant reports. This method is used in place of an automated in-bed algorithm, which was not developed for hip accelerometers or for use in older adult samples. Older women have lower levels of activity throughout the day and especially at night, which may lead an algorithm to misclassifying hours or sedentary behavior as sleep time. In addition, our participant sample was purposefully recruited to have larger numbers of racial-ethnic minorities including African Americans and Hispanics who tend to report, on average, shorter sleep durations<sup>15</sup> and have higher prevalence of CVD risk factors.<sup>53</sup> Prior studies that included objective assessment of sleep duration typically

only have compared two racial-ethnic groups (e.g., non-Hispanic whites vs. African Americans), and not large proportions of women from racial-ethnic groups with wide age ranges.<sup>35,54</sup>

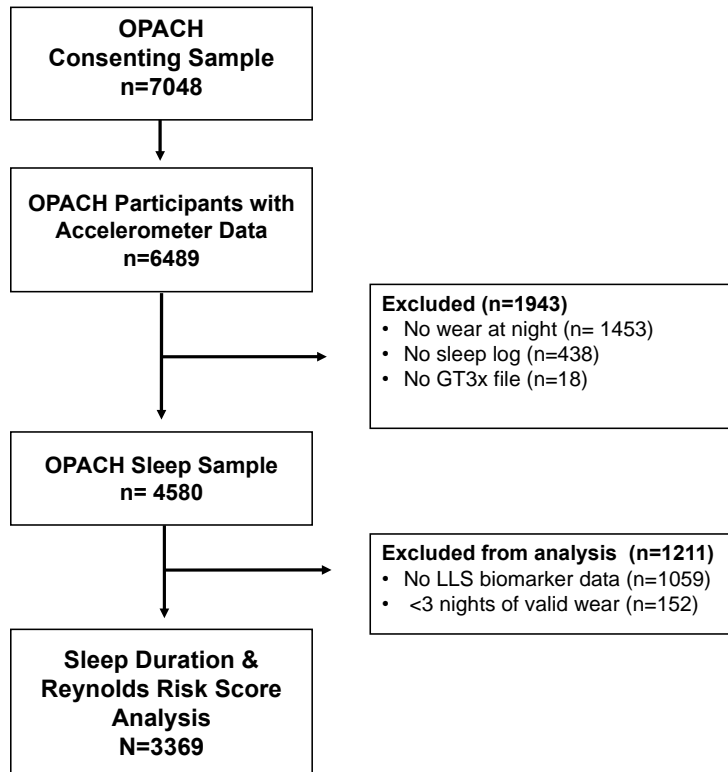
This study has some limitations. As is common with sleep studies, the amount of sleep that leads to the best health outcomes can vary by individual. These study results and conclusions drawn regarding sleep duration and CVD risk reflect the risk associated with average sleep durations across a large sample of women. Additionally, our study sample includes only postmenopausal older women, and therefore is not generalizable to the population as a whole. Further, our exposure variable, sleep duration, was only assessed at one time point, and therefore the influence that changes in sleep duration over time have on the relationship between sleep duration and CVD risk cannot be evaluated in this study. The relationship between accelerometer-measured sleep duration and CVD risk was not the primary aim of the OPACH study and therefore there was not implementation of data collection screening to ensure women wore the accelerometer device overnight. Our sample was reduced substantially by the 1,943 women without sleep data and the 1059 women without biomarker data who were excluded from this analysis. It is likely that as health worsens and comorbidities increase with age, sleep duration and quality are impacted, as seen previously in longitudinal studies of sleep duration and incident CVD.<sup>11,33,55</sup> Lastly, while we included sleep medications and sleep disturbance in our analysis, we were not able to include a diagnosis of obstructive sleep apnea (OSA). This was not assessed in the LLS questionnaire. Evidence demonstrates that OSA is a risk factor for many cardiometabolic conditions, including obesity, hypertension, insulin resistance, and CVD.<sup>56,57</sup> Not being able to eliminate this possible mediator is a limitation of this study. However, previous evidence suggest that the bulk of OSA remains undiagnosed and untreated, particularly in the elderly, so we believe that our findings still have real world applicability. Finally, because

we employed hip accelerometers, which provide a valid assessment of total sleep duration, we were not able to examine aspects of sleep quality. Previous research suggests that sleep quality is also a possible risk factor for CVD.<sup>4</sup> More research is need to examine objectively measured sleep quality and CVD risk in large diverse cohorts of older women.

The results of this study support the growing evidence that sleep duration is a potential modifiable risk factor for CVD. As the incidence of CVD continues to increase in the aging population of women in the United States, it is important to identify additional risk factors that can be targeted in order to enhance CVD prevention interventions. While the length of sleep for optimal health is not completely clear at present and may vary by individual, this study highlights the importance of sleep duration for cardiovascular health.

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Chapter 2, in full, has been submitted for the publication of the material. Co-authors include Drs. Jacqueline Kerr, Atul Malhotra, Linda Gallo, Elva Arredondo, Loki Natarajan, Michael J. LaMonte, Marcia L. Stefanick, Katie L. Stone, and Andrea Z. LaCroix. The dissertation author was the primary investigator and author of this material.



**Figure 2.1:** OPACH study participant flow diagram



**Table 2.1:** Participant characteristics for the OPACH cohort by quartiles of average nightly sleep duration

	Overall N=3369 Mean $\pm$ SD N (%)	Average Nightly Sleep Duration (hours/night)				Trend, P- value
		<7 hours n=517	7-8 hours n= 975	8-9 hours n=1149	>9 hours n=728	
<b>Age, years</b>	78.9 $\pm$ 6.7	77.6 $\pm$ 6.5	78.3 $\pm$ 6.6	79.4 $\pm$ 6.7	80.0 $\pm$ 6.8	<.01
63-69	334 (9.9)	67 (13.0)	110 (11.3)	100 (8.8)	57 (7.8)	<.001
70-79	1295 (38.4)	234 (45.3)	391 (40.1)	416 (36.2)	254 (34.9)	
80-89	1591 (47.2)	205 (39.7)	444 (45.5)	570 (49.6)	372 (51.1)	
$\geq$ 90	149 (4.4)	11 (2.2)	30 (3.1)	63 (5.5)	45 (6.2)	
<b>Race-ethnicity</b>						<.001
White	1797 (53.3)	208 (40.2)	531 (54.5)	667 (58.1)	391 (53.7)	
Black	1007 (29.9)	201 (38.9)	278 (28.5)	300 (26.1)	228 (31.3)	
Hispanic	565 (16.8)	108 (20.9)	166 (17.0)	182 (15.8)	109 (15.0)	
<b>Education</b>						0.49
High school or less	694 (20.6)	98 (19.1)	202 (20.8)	228 (20.0)	166 (23.0)	
Some college	1300 (38.6)	191 (37.2)	379 (39.0)	455 (39.8)	275 (38.1)	
College graduate	1357 (40.3)	225 (43.8)	391 (40.2)	460 (40.2)	281 (38.9)	
<b>Health Behaviors</b>						
<b>Alcohol Intake in past 3 months</b>						
$\geq$ 5 drinks/wk	362 (10.8)	45 (9.4)	121 (13.4)	123 (11.6)	73 (10.9)	<0.05
<b>Physical Activity mins/day</b>	344.4 $\pm$ 97.7	384.1 $\pm$ 108	366.5 $\pm$ 92.7	338.0 $\pm$ 87.8	296.8 $\pm$ 90.3	<.001
<b>Sleep Disturbance Score</b>	6.3 $\pm$ 4.5	5.8 $\pm$ 4.5	6.1 $\pm$ 4.3	6.3 $\pm$ 4.5	6.8 $\pm$ 4.6	<0.05
<b>Sleep Medication Use</b>						
$\geq$ 3 times/wk	206 (6.1)	21 (4.1)	57 (5.9)	69 (6.0)	59 (8.1)	<0.05
<b>Health Characteristics</b>						
<b>BMI, Kg/m<sup>2</sup></b>	27.9 $\pm$ 5.7	28.5 $\pm$ 5.8	28.0 $\pm$ 5.8	27.5 $\pm$ 5.5	27.7 $\pm$ 5.5	0.97
$\geq$ 30 (obese)	994 (29.5)	168 (32.7)	293 (30.2)	326 (28.6)	207 (28.7)	0.23
<b>Physical Functioning 0-100 score</b>	68.4 $\pm$ 25.8	70.7 $\pm$ 25.6	70.3 $\pm$ 25.0	69.4 $\pm$ 24.5	62.7 $\pm$ 28.0	<.001
<b>Comorbidity Index <math>\geq</math>2 comorbidities</b>	610 (18.1)	79 (15.3)	149 (15.3)	213 (18.5)	169 (23.2)	<.001
<b>Depression Score range 0-1</b>	0.03 $\pm$ 0.1	0.03 $\pm$ 0.1	0.03 $\pm$ 0.1	0.02 $\pm$ 0.1	0.03 $\pm$ 0.1	<0.05
<b>Self-report Health</b>						
At least good	2825 (83.9)	449 (93.9)	830 (92.1)	964 (90.6)	582 (86.7)	<.001
<b>Reynolds Risk Score Components</b>						
<b>Total Cholesterol mg/dL</b>	197.3 $\pm$ 39.6	196.1 $\pm$ 39.8	196.5 $\pm$ 38.1	198.0 $\pm$ 40.4	198.2 $\pm$ 40.2	0.57
<b>HDL Cholesterol mg/dL</b>	60.8 $\pm$ 15.2	61.5 $\pm$ 14.8	60.5 $\pm$ 15.2	60.9 $\pm$ 15.0	60.3 $\pm$ 15.5	0.94
<b>Systolic Blood Pressure</b>	125.6 $\pm$ 14.5	125.3 $\pm$ 13.9	125.9 $\pm$ 14.5	125.3 $\pm$ 14.7	125.8 $\pm$ 14.7	0.96
<b>High-sensitivity CRP mg/L</b>	3.6 $\pm$ 8.8	3.4 $\pm$ 5.0	3.2 $\pm$ 5.8	3.8 $\pm$ 12.1	4.1 $\pm$ 8.0	0.07
<b>History of diabetes</b>	655 (19.4)	118 (22.8)	173 (17.7)	211 (18.4)	153 (21.0)	0.06
<b>Family History of CVD</b>	308 (9.1)	38 (7.4)	95 (9.7)	103 (9.0)	72 (10.0)	0.40
<b>Current smoker</b>	78 (2.3)	19 (3.7)	27 (2.8)	18 (1.6)	14 (1.9)	<0.05

BMI, body mass index; min, minutes. Note: Numbers do not sum to total due to missing data

**Table 2.2:** Estimated Reynolds risk score for sleep durations (N=3369)

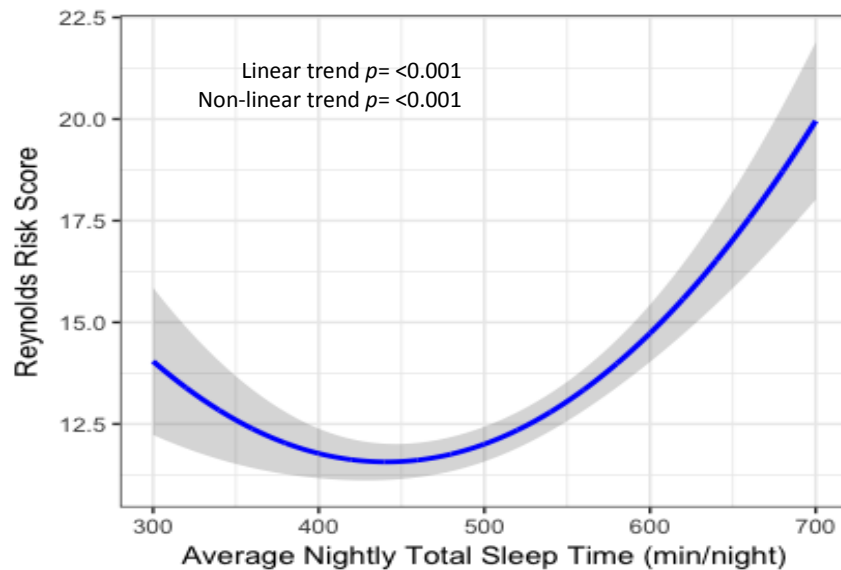
Sleep Duration Hours (mins)	Estimated Reynolds Risk Score		
	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 3 <sup>c</sup>
<b>5 Hours (300 mins)</b>	14.04	15.04	14.55
<b>6 Hours (360 mins)</b>	12.38	13.40	13.18
<b>7 Hours (420 mins)</b>	11.62	12.39	12.34
<b>8 Hours (480 mins)</b>	11.76	12.02	12.03
<b>9 Hours (540 mins)</b>	12.80	12.27	12.24
<b>10 Hours (600 mins)</b>	14.73	13.16	12.99
<b>11 Hours (660 mins)</b>	17.57	14.68	14.26
<b>p value<sup>d</sup></b>	<0.001	<0.001	<0.01

<sup>a</sup> Adjusted analyses include race/ethnicity and education

<sup>b</sup> Adjusted analyses include race/ethnicity, education, alcohol intake, physical activity, sleep medications, and sleep disturbances

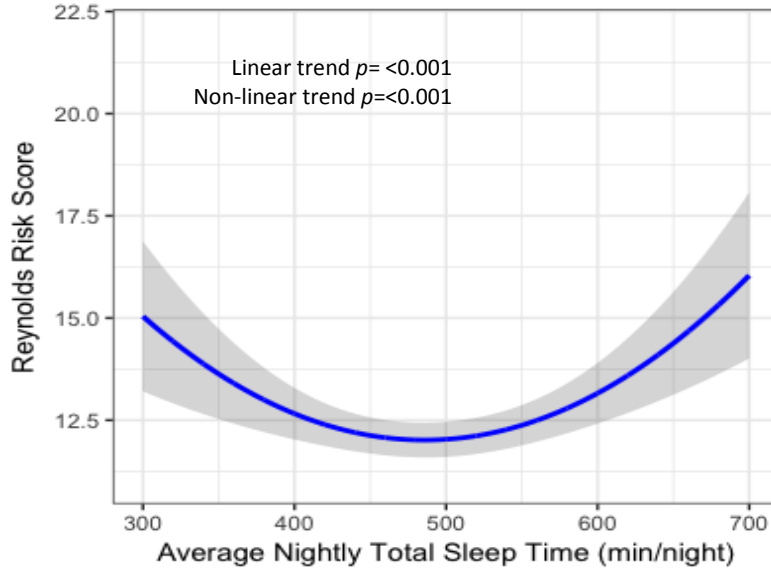
<sup>c</sup> Adjusted analyses include race/ethnicity, education, alcohol intake, physical activity, sleep medications, sleep disturbances, BMI, physical functioning, comorbidities, depression, and self-rated health

<sup>d</sup> p values presented for quadratic term in the model

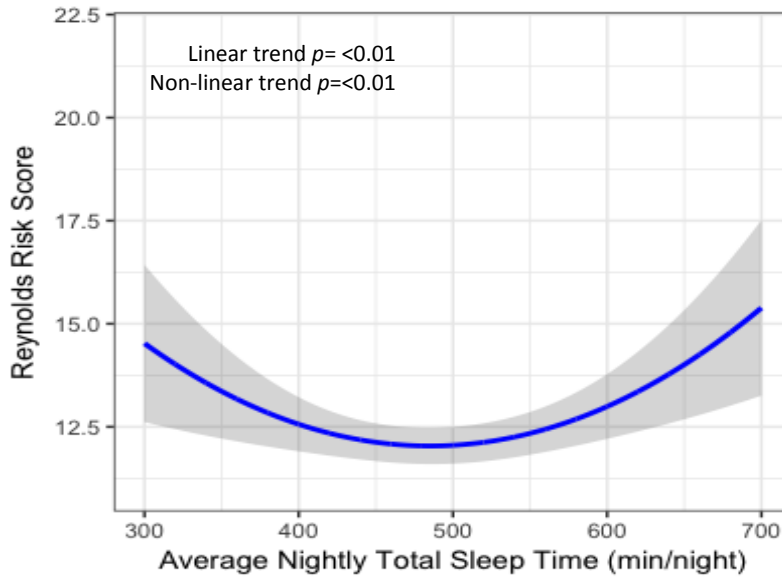


**Figure 2.2:** Sleep duration and Reynolds Risk Score in the OPACH sleep cohort after adjustment.<sup>1</sup>

<sup>1</sup> Model adjusted for race/ethnicity and education



**Figure 2.3:** Sleep duration and Reynolds Risk Score in the OPACH sleep cohort after further adjustment.<sup>2</sup>



**Figure 2.4:** Sleep duration and Reynolds Risk Score in the OPACH sleep cohort after final adjustment.<sup>3</sup>

<sup>2</sup> Model adjusted for race/ethnicity, education, alcohol use, sleep medications, sleep disturbances, and total minutes of accelerometer measured physical activity

<sup>3</sup> Model adjusted for race/ethnicity, education, alcohol use, total minutes of accelerometer measured physical activity, sleep medications, sleep disturbances, BMI, physical functioning, comorbidity index score, depression, and self-rated health.

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## CHAPTER 3

### Accelerometer-Measured Sleep Duration and Cardiovascular Incidence in Post-Menopausal Older Women: Evidence from the Women's Health Initiative

#### ABSTRACT

**Background:** Epidemiological studies have found an increased risk of incident CVD for self-reported short sleep duration or self-reported long sleep duration when compared to sleep durations of 8-9 hours. To advance the understanding of the relationship between sleep duration and CVD, there is a need for more research to examine the relationship between sensor-measured sleep duration and CVD risk in an older population of women, and to determine if insufficient sleep duration is a CVD risk factor that holds promise for future CVD prevention strategies.

**Methods:** Participants from the Women's Health Initiative OPACH Study (n=4203, mean age=78.5, 33.4% Black, 17.0% Hispanic) wore accelerometers on the hip for up to 7 days, completed a daily sleep log, and were followed for incident CVD for up to 5 years. Sleep duration derived from accelerometer data was calculated using a visual inspection protocol. Self-reported sleep duration was averaged from daily sleep logs. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CIs) for both measures of sleep duration in relation to incident coronary heart disease (CHD) and incident CVD. Fully adjusted models included age, race-ethnicity, smoking, education, comorbidities, physical function, self-rated health, and total physical activity.

**Results:** In minimally adjustment models, neither short or long sleep duration, measured by accelerometry, were associated with increased risk of CVD. In contrast, log-based long sleep duration (>9 hours/night) was associated with increased risk of CVD, in the model adjusted for

age, race-ethnicity, education, and smoking (HR: 1.27; CI:1.01,1.61). In the fully adjusted model, this association between log-based long sleep duration and CVD was no longer significant. The mean difference in accelerometer-measured sleep duration and log-based self-reported sleep duration was 18 minutes (SD:43.88 minutes) and physical functioning (B:-0.18, p: <0.001) and total minutes of PA (B:0.05, p: <0.001) were significantly associated with differences in sleep duration estimates.

**Conclusions:** After adjustment for demographics and markers of health status, neither short or long sleep durations were associated with an increased risk of CHD or CVD over the 5-year period in this sample of older women. Future studies with multiple time points of sleep assessment and assessment of sleep disorders are necessary to explore further the relationship between sleep and CVD risk.

## INTRODUCTION

Over half of older adults in the United States experience disturbed sleep, including shorter or longer sleep durations, increased frequency of awakenings, difficulty maintaining sleep, decreased sleep efficiency, and changes to sleep architecture.<sup>1-5</sup> Older women are more likely to report sleep disturbances and poor sleep quality than their male counterparts.<sup>1,3,5</sup> In a Women's Health Initiative (WHI) study examining sleep disturbances in over 98,000 older women, weekly night time awakenings and daytime sleepiness were reported by over 75% of the women in the study.<sup>6</sup> The large proportion of older adult women who regularly experience poor or insufficient sleep may be at risk of adverse health outcomes and pose a major public health concern.<sup>7</sup>

Emerging evidence suggests that sleep duration may be a cardiovascular disease (CVD) risk factor.<sup>8,9</sup> The American Heart Association estimates that more than one in three US women has some form of CVD, and an additional 90% of women are currently living with one or more risk factors.<sup>10</sup> As women age, their risk of cardiovascular disease (CVD) increases. Older women over the age of 80 years are at greatest risk for CVD, with higher incidence of CVD events than men of the same age.<sup>11</sup> Recent studies have focused on the cardiometabolic associations of sleep quality and sleep duration, including a number of cross-sectional and prospective studies demonstrating that self-reported short and long sleep durations are predictors of incident cardiometabolic conditions such as: type 2 diabetes, hypertension, metabolic syndrome, and obesity.<sup>12-17</sup> Further, prospective epidemiological studies have found an increased risk between 30-50% of incident CVD for self-reported short sleep duration (<6 hours) or self-reported long sleep duration (>9 hours) when compared to sleep durations of 8-9 hours.<sup>18-22</sup> Reviews of the existing research, based on self-reported measures, have concluded that inadequate sleep

duration and poor sleep quality are associated with increased development, progression, and severity of CVD and CVD comorbidities.<sup>9</sup>

Our understanding of the relationship between sleep duration and CVD remains incomplete due to the limitations of the existing research. Previous studies have consisted primarily of cross-sectional study designs, or have been limited in the reliance on one-item self-reported measures of sleep duration.<sup>23,24</sup> Studies have demonstrated that when sleep duration is assessed by one survey item asking participants to recall their “usual” sleep, it is significantly overestimating sleep duration when compared to wrist actigraphy.<sup>25,26</sup> Monitoring sleep duration through body-worn sensors, e.g. accelerometers, is considered more accurate than self-reported sleep duration or sleep logs alone,<sup>27</sup> especially in older adult populations where cognitive issues affecting recall may be present.<sup>28</sup> Another weakness of previous studies includes samples primarily consisting of middle-aged non-Hispanic white adults. While CVD incidence is higher in older women, and African American and Non-white Hispanic populations,<sup>11</sup> most published studies on sleep and CVD risk have not adequately represented women from these groups.<sup>8,9</sup> The 2016 scientific statement from the American Heart Association on sleep and cardiometabolic health urges future research to include both women and minorities in study samples and for more objective measurements of sleep.<sup>8</sup>

The objective of the current study was to prospectively examine associations of sleep duration, measured by self-reported sleep log and accelerometry, with incident CHD and CVD events over up to 5 years of follow-up in a racial-ethnically diverse cohort of older women. We postulated, a u-shaped relationship between sleep duration and CVD events, with fewer hours of sleep and excess hours of sleep being associated with an increased risk of CVD.

## METHODS

### *Study Population*

The Women's Health Initiative (WHI) is a national study focusing on healthy aging, morbidity, and mortality among postmenopausal women that recruited women for participation in a Clinical Trial Program or an Observational Study from 1993-1998.

Women in the present study were enrolled for participation in the Objective Physical Activity and Cardiovascular Health (OPACH) study, a WHI ancillary study. The aims of the OPACH study were to examine prospectively the relationship between accelerometer-measured physical activity and incidence of CVD in older women. Details on OPACH recruitment and methodology have been previously published.<sup>30</sup>

Between 2012-2013, women participating in a WHI extension study, the Long Life Study (LLS), completed in-home health assessments. During this visit, fasting blood draws, information regarding personal health and lifestyle, anthropometric measurements, and blood pressure were obtained. A subset of LLS participants (N=7048) were consented and enrolled in the OPACH study. OPACH participants received GT3x accelerometer devices and were asked to wear them on their waist for 24 hours per day over a 7-day period. Additionally, participants were asked to complete sleep logs and report their in-bed time and out-of-bed time for the 7-day accelerometer wear period.

Of the 7048 women who were OPACH consented participants, 6,489 women returned their devices and provided at least one day of accelerometer data. Of these, 4,204 met eligibility criteria for inclusion in this analysis, including completion of at least 3 nights of valid accelerometer data, and a completed sleep log (Figure 3.1). Participants with fewer than 3 nights of accelerometry data, or those who were missing a completed sleep log were excluded from this

analysis. Women with an myocardial infarction (MI) or stroke before OPACH baseline (n=520) were also excluded. In consideration of night to night sleep variation, previous sleep studies have demonstrated that one night of accelerometer wear is not sufficient to assess regular sleep habits.<sup>31</sup> Additionally, previous cohort studies examining cardiovascular health have defined valid wear as three nights.<sup>32</sup>

### ***Coronary Heart Disease and Cardiovascular Disease Events***

The primary endpoint was defined as a major fatal or non-fatal CVD event including incident coronary heart disease (CHD), including MI or coronary death, or new CVD event including hospitalized angina, coronary artery bypass graft (CABG), congestive heart failure, revascularization, percutaneous transluminal coronary angioplasty (PTCA), stroke, or fatal CVD event. These events were combined to examine the associations of sleep duration with incident CHD and CVD. Adjudicated incident CVD outcomes were initially identified through annual follow-up contacts and then verified by trained staff through medical records and death certificates. The WHI protocol for outcome diagnosis and adjudication have been previously described.<sup>33</sup> Participants were followed for first occurrence of a CVD outcome, and those individuals who did not develop CVD were censored at the date of death or last contact.

### ***Log-Based Sleep Duration***

Self-reported sleep duration was assessed with a participant sleep log. Participants were asked to complete a daily sleep log during the 7-day accelerometer wear period, to record their time into bed for the night and time out of bed in the morning for each night. Sleep logs were returned in the mail with the accelerometer device. A nightly sleep duration (total minutes) was calculated as the total amount of time in bed the participant reported. Mean sleep duration was calculated across the available nights of self-reported sleep duration (ranging from 3-7 nights) to

create an average nightly self-reported sleep duration variable. The log-based sleep duration was selected for this analysis over a 1-item self-report measure of usual sleep duration as the 7-day sleep logs provide real time self-reported information over the same 7 days as the accelerometer measured sleep duration. Validation studies have shown that a 1-item survey measure and 1-week sleep log have a .79 correlation.

### ***Accelerometer Measured Sleep Duration***

Accelerometer measured sleep duration was assessed with the hip-worn triaxial accelerometer (Actigraph GT3X+; Pensacola, FL). Participants wore the accelerometer device on their hip, 24 hours a day for 7 consecutive days, except for time spent bathing or swimming. Data were recorded in 1-second epochs collected at a frequency of 30 Hertz. Wrist-worn accelerometer devices are more standard for sleep assessment, however hip-worn accelerometers are the norm for physical activity studies like OPACH.<sup>34,35</sup> Hip accelerometers have been shown to provide valid assessments of total sleep duration against the gold standard polysomnography.<sup>35,36</sup>

Upon device return, raw data were processed using ActiLife version 6.11 software. Raw data were condensed to 60 second AGD files. AGD files were scored for sleep variables using a standard visual inspection protocol. For each night of wear, a trained member of the research team identified the primary sleep window using the participant reported in-bed and out of bed time from sleep logs and visual review of the data. This procedure is adapted for hip devices from a protocol shown previously to have high inter-rater reliability.<sup>37</sup> The validated Cole-Kripke algorithm<sup>38</sup> was applied to classify each minute of the sleep interval as sleep or wake. Estimates of nightly sleep duration were derived as the total amount of time classified as sleep (minutes/night) during the primary sleep period. Mean sleep duration was calculated across the

available nights of scored sleep (ranging from 3-7 nights) to create an average nightly sleep duration variable.

### *Covariates*

WHI questionnaires were used to obtain information on participant demographics, education, smoking, self-reported physical functioning, self-rated health, depressive symptoms, self-reported sleep disturbances, and history of chronic conditions.

Education was categorized into 3 levels: high school or less, some college, college graduate or more. Smoking was measured with 1-item assessing if the participant is a current smoker, response options were “yes” or “no”. Physical functioning was assessed using the 10-item physical function score of the RAND 36-item health survey.<sup>39</sup> The physical function score has a range of 0-100 with higher scores indicating better function. Self-rated health was assessed with 1-item from the WHI lifestyle questionnaire asking participants “In general would you say your health is...”. Response options ranged on a 5-point scale from “excellent” to “poor”. Depression was assessed with the WHI Burham adaptation Scale,<sup>40</sup> of the CES-D scale. Scale scores ranged from 0-1 with higher values indicating a higher presence of depressive symptoms. Sleep disturbances were assessed with the WHI Insomnia Rating Scale (WHIIRS).<sup>41</sup> A scale score is calculated from the five item scores (0-4) to create a global sleep disturbance score ranging from 0-20. A higher WHIIRS score is reflective of greater presence of sleep disturbances and has been shown to be predictive of CVD.<sup>24</sup> The use of sleep medications was assessed with 1-item assessing in the last 4 months, how many times per week a participant used sleep medications. Response options ranged from “None in the past 4 weeks” to “5 or more times per week”. A comorbidity index variable was created using the self-report of chronic conditions



collected in the baseline survey. The index included self-report of history of chronic obstructive pulmonary disease (COPD), history of osteoarthritis, history of cerebrovascular disease, history of cancer, history of cognitive impairment, and history of hip fractures. The number of conditions was summed to create a comorbidity index score (0-6).

The Reynolds Risk Score (RRS), is calculated using age, systolic blood pressure (SBP), high-sensitivity C-reactive protein (CRP), total and HDL cholesterol, diabetes mellitus status, smoking status, and family history of premature myocardial infarction. The score is calculated as an estimate for 10-year predicted CVD risk.<sup>42</sup> At the LLS home visit, fasting blood measures used in the RRS calculation (including CRP, total cholesterol, and HDL cholesterol) were obtained. Resting blood pressure (BP) was measured after a 5-minute rest period using an aneroid sphygmomanometer and cuff size based on measured arm circumference. Diabetes mellitus status, smoking status, and family history of premature myocardial infarction were assessed using the LLS questionnaire. Total daily physical activity minutes were calculated from the GT3x accelerometer when summed vector magnitude counts exceeded 8 counts per 15 seconds.<sup>43</sup>

### ***Statistical Analysis***

Survival analyses were completed to assess the association between baseline sleep duration and incident CHD events and new CVD events using Cox proportional hazard regressions. Both log-based and accelerometer-measured sleep durations were examined categorically, as short sleep (<8 hours) and long sleep (>8 hours) compared to healthy sleep (8-9 hours). These categories were selected based on the distribution of sleep duration in the cohort. A series of progressive adjustment models were evaluated in the analysis: the first minimally

adjusted for age and race-ethnicity, the second added adjustment for education and smoking, the third added adjustment for self-rated health, comorbidities, and physical functioning, and the final model added an additional adjustment for total minutes of physical activity. Secondary models added adjustment for self-reported sleep disturbances and depression. There was no multi-collinearity between independent variables in the models.

Sensitivity analyses were conducted to determine if how the sleep duration categories were defined impacted the results of the hazard ratio models. In these additional analyses short sleep was defined as either <7 hours/night and <6 hours/night and long sleep defined as >9 hours/night. Participants who averaged 7-8 or 8-9 hours/night served as the reference category. Further stratified analyses were conducted (stratified by RRS, total minutes of MVPA, and physical functioning) to assess possible confounders and to see if the relationships examined in the cox proportional hazard analyses remained consistent.

The difference in log-based sleep duration and accelerometer-measured sleep duration was calculated. Linear models adjusted for age and race-ethnicity were used to explore the possible predictors of the discordance in the measures.

## **RESULTS**

The mean age of the 4204 women was 78.5 years (range 63-99; Table 3.1). Overall, 49.5% of women were white, 33.4% black, and 17% Hispanic. The majority of women had at least some college education (79.5%). Women had a mean BMI of 28.0 kg/m<sup>2</sup>. On average, women reported a sleep disturbance score of 6.27, out of 20. The average physical functioning score was 69.6 and 13.9% of the sample reported 2 or more comorbid conditions. Only 2% of the women reported current smoking.

### ***Sleep Duration and Baseline Characteristics***

When measured by sleep log, 35% of women in the cohort self-reported sleep durations between 8-9 hours, while only 32% had accelerometer-measured sleep durations between 8-9 hours. The proportion of women with log-based long sleep durations (>9 hours) was greater than the proportion of women with accelerometer-measured long sleep durations (30% vs 23%). For both measures of sleep duration, long sleepers (>9 hours) were more likely to be older women with a mean age of 79.4 years, and were more likely to be white women (47.9% for log-based, 50% for accelerometer measured) compared to women who had short sleep durations (mean age: 77.7 years; proportion white: 44% for log-based and accelerometer measured). Long sleepers also had the lowest levels of total daily physical activity (mean minutes: 307.5 for log-based, 296.3 for accelerometer measured), highest sleep disturbance scores (mean: 6.7 for log-based, 6.8 for accelerometer measured), and the lowest physical functioning scores (mean: 63.2 for log-based, 62.7 for accelerometer measured) compared to women in the short or healthy (8-9 hours) sleep duration categories. Across both measures short sleepers (<8 hours) were more likely to report excellent self-rated health (55.2% for log-based, 53.9% for accelerometer-measured), and more likely to be current smokers (3.2% for log-based, 2.9% for accelerometer-measured) compared to women with healthy sleep durations (self-rated health: 54.7% for log-based, 53.3% for accelerometer-measured; smokers: 1.5% for log-based, 1.9% for accelerometer-measured).

On average, participants log-based sleep durations were 18 minutes longer (SD:43.88 minutes, range: 0-359 minutes) than their accelerometer-measured sleep duration. The two measures appear to estimate sleep duration similarly and were positively correlated with a Pearson's correlation of  $r=0.83$  ( $p<0.001$ ; Figure 3.2). In the linear model adjusted for age and race/ethnicity, physical functioning scores (B:-0.18,  $p<0.001$ ) and total minutes of PA (B:0.05,  $p<0.001$ ) were significantly associated with the difference in sleep duration estimates,

indicating that women with lower physical functioning scores and higher total minutes of PA had greater differences between their sleep duration estimates.

### ***Sleep Duration and incident CHD and new CVD events***

Within an average follow-up period of 3.5 years (range 0.01 – 4.91 years), a total of 143 incident cases of CHD (MI or coronary death) and 536 CVD events occurred. For log-based sleep duration, after adjustment for age and race/ethnicity, the risk of incident CVD was significantly higher for women in the long sleep category (>9 hours) [Hazard Ratio (HR): 1.27, 95% confidence interval (CI): 1.01,1.61], compared with women in the healthy sleep category (8-9 hours), but did not differ significantly for women in the short sleep category (<8 hours; Table 3.2). These results remained consistent after adjustments for education and smoking. When further adjusted for comorbid conditions, physical functioning, and self-rated health the risk of CVD was no longer significantly higher for women in the long sleep category when compared to women in the healthy sleep category [HR: 1.13, CI: 0.89,1.43]. The increased risk of incident CHD after adjustment for age and race/ethnicity was not significant for long sleepers [HR: 1.37, CI: 0.87-2.16] or for short sleepers [HR: 1.11; CI: 0.69-1.80] when compared with women with log-based sleep duration in the 8-9 hour category. Additional adjustment for sleep disturbances produced similar results.

For accelerometer-measured sleep duration, after adjustment for age and race/ethnicity, risk of incident CVD was similar for women in the long sleep category (>9 hours, HR:1.08; CI:0.84-1.80) or the short sleep category (<8 hours, HR: 1.06; CI:0.85-1.33) as compared to women in the healthy sleep category (8-9 hours). These results remained null after additional adjustment for education, smoking, comorbid conditions, physical functioning, self-rated health and sleep disturbances. For CHD, after adjustment for age and race-ethnicity there was no

significant increased risk for women with accelerometer-measured long sleep duration [HR: 0.80, CI: 0.52-1.21] or women with short sleep duration [HR: 0.76; CI: 0.46-1.21] when compared with women with sleep duration in the 8-9 hour category.

Sensitivity analyses showed that, the multivariable-adjusted associations for both log-based sleep durations and accelerometer-measured sleep durations were similar to the results of the primary analysis when sleep was categorized with short sleep defined as <6 or <7 hours, and long sleep as >9 hours. To further evaluate the influence of health status at baseline, we stratified these associations according to median RRS, median total PA, and median physical functioning. The results of the stratified analyses were similar to the primary analyses for the RRS median split (log-based: p-trend=0.2; accelerometer measured: p-trend=0.6) and median total PA split models (log-based: p-trend=0.2; accelerometer measured: p-trend=0.8). When the log-based sleep duration analyses were stratified by physical functioning, in the low physical functioning group the risk of incident CVD was significantly higher for women in the long sleep category (>9 hours, HR: 1.42; CI: 1.07-1.88 p-trend: 0.01], compared with women in the healthy sleep category (8-9 hours). For women in the high physical functioning group, neither short or long sleep was associated with increased risk of incident CVD.

## **DISCUSSION**

To our knowledge this is the first study to examine the relationship of accelerometer-measured sleep duration and incident CVD in a cohort of older women. After adjustment for demographics and markers of health status, neither short or long sleep durations were associated with an increased risk of incident CHD or new CVD events. These results were consistent for

both self-reported log-based sleep duration and accelerometer-measured sleep duration after a series of progressive adjustments.

Previous studies have shown associations between one-item self-reported short and long sleep duration and increased risk for cardiometabolic conditions that are risk factors for CVD, including: incident type 2 diabetes, obesity, and metabolic syndrome.<sup>13,14,17,44</sup> The relationship between one-item self-reported sleep duration and incident CVD and CHD has been examined in several studies with more varied results, with some studies showing increased risk for both short and long sleep durations, and some studies showing no increased risk across sleep durations.<sup>18,24,45</sup> In the OPACH cohort, short sleep durations (<6, <7, or <8 hours), measured either by sleep log or accelerometer, were not related to increased risk of CVD. The difference in our results could be attributed to the age of the cohort and the overall longer sleep durations observed. In our analysis, women with shorter sleep durations were younger, and appeared to be overall healthier, with better self-reported health, higher physical functioning, and higher total PA than women in the 8-9 hours/night or >9 hours/night categories.

The lack of association of log-based sleep duration with incident CHD and new CVD events in this study are consistent with a previous WHI study examining survey-reported sleep duration and CVD incidence in older women. Among 86,329 women between the ages of 50 and 79 years, a modest increase in risk was seen for short (<7 hours) and longer sleepers (>10 hours) in minimally adjusted models; however, the increase in risk was not significant after adjustment for socioeconomic status, lifestyle behaviors, and comorbid conditions.<sup>24</sup> The authors suggested that in part the increase in risk was due to comorbid conditions in the population. In our analysis, self-reported long sleep duration was associated with increased risk when compared to sleep durations of 8-9 hours; however, this relationship was no longer significant after adjustments for

comorbid conditions. Further, this relationship was not found in any of the accelerometer-measured sleep duration models. These results suggest that the increased CVD risk associated with self-reported long sleep duration may be attributed to poor health status and not sleep duration. Women who reported long sleep durations were older, had less total physical activity, lower physical functioning, higher sleep disturbances, more comorbid conditions, and were less likely to report excellent health. Further, when we explored predictors of the difference in the log-based self-report and accelerometer measured sleep, poorer physical functioning and higher physical activity were significantly related to an overestimation in sleep duration. Previous research has suggested that how a participant reports sleep duration may be impacted by other factors including: socio-economic status, living conditions, other health behaviors, and overall health status.<sup>46</sup> This difference in log-based sleep when compared to accelerometer-measured sleep, may be a reflection of the women's overall health status, and not necessarily reflective of sleep duration. For older women, reporting longer periods in bed may not actually reflect time spent sleeping, but the presence of sleep disorders, such as obstructive sleep apnea, or comorbid conditions such as depression or mental health outcomes, which are all associated with longer sleep durations.<sup>47</sup>

While the study results do not support a relationship between sleep duration and incident CVD, they do not contradict the role that sleep plays in health. In our cohort, whether log-based or by accelerometer, long sleepers had overall poorer health status than individuals in the 8-9 hour sleep category. Previous studies support that the relationship between sleep duration and health may be bi-directional, with poor sleep leading to poor health, and poor health leading to poor sleep.<sup>1,8,47</sup> In this cohort of older women, while we may not be able to identify an optimal sleep duration associated with lower CVD incidence, we should still consider how sleep may

contribute to other health outcomes, including those that are in the pathway to CVD. A previous analysis completed in this cohort demonstrated that sleep duration, measured by accelerometer, was associated with markers of cardiometabolic health and 10-year estimated risk of CVD. In addition to the relationship between sleep duration and markers of cardiometabolic health, evidence demonstrates that sleep is related to other health behaviors that are associated with CVD risk, including diet, PA, and sedentary behavior.<sup>8,48</sup> In the OPACH cohort, previous analyses have found that light PA was protective against incident CVD and high levels of sedentary behavior were associated with increased risk of incident CVD.<sup>49,50</sup> It is possible in this cohort, as in previous studies, that these activities may be interrelated and that sleep duration is associated with daily PA and sedentary behavior.<sup>48,51,52</sup>

The present study has some limitations. Our study cohort included only older women over the age of 63 years, and therefore is not generalizable to the population as a whole. These women make up a unique subpopulation who are at increased risk for CVD, but who have also survived (mean age of 78.5 years) to later life. As discussed previously, health worsens with age as does sleep quality, therefore it is difficult to untangle this complex relationship. An assessment of sleep disorders, such as obstructive sleep apnea (OSA) was not included in our analysis as they were not assessed in the LLS questionnaire. Previous research suggests that OSA is a risk factor for CVD,<sup>53,54</sup> and a possible confounder in the relationship between sleep duration and CVD.<sup>55</sup> Without the assessment of sleep disorders, including OSA, we could not disentangle sleep duration with or without a concomitant sleep diagnosis. However, given the null results observed in this investigation, confounding by OSA seems unlikely. Finally, because we employed hip accelerometers, valid for total sleep duration only, we were not able to examine aspects of sleep quality, beyond self-reported sleep quality. It is important to note that previous



studies have found that hip accelerometers do provide longer estimates of sleep duration than both PSG and wrist-worn accelerometers.<sup>56</sup> Future research is needed to confirm these results, examining sleep duration and quality, assessed by wrist actigraphy or polysomnography, and CVD risk in large diverse cohorts of older women.

In summary, this analysis contributes to the existing literature by examining sleep duration, measured both by sleep logs and accelerometers in the same cohort of women, and incident CVD. After adjustment for age, race-ethnicity and health status, neither women with short sleep or long sleep durations had an increased risk of CVD, compared to women with sleep durations between 8-9 hours. The increased risk that was seen for women with long self-reported sleep duration in the minimally adjusted models may be explained by other markers of poor health status, including physical functioning or lower levels of total PA. Future studies with multiple time points of sleep assessment and assessment of sleep disorders are necessary to explore further the relationship between sleep and CVD risk.

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**Table 3.1:** Participant characteristics for the OPACH cohort by measure sleep duration category

	Overall Sample	Log-Based Sleep Duration			Accelerometer Sleep Duration		
	N=4204 mean ± SD n (%)	<8 hours n=1428	8-9 hours n=1476	>9 hours n=1299	<8 hours n=1857	8-9 hours n=1373	>9 hours n=974
<b>Age, years</b>	78.5 ± 6.8	77.7 ± 6.6	78.5 ± 6.8	79.4 ± 6.7	77.7 ± 6.6	78.9 ± 6.8	79.4 ± 6.8
63-69	469 (11.2)	189 (13.2)	174 (11.8)	106 (8.2)	240 (12.9)	144 (10.5)	85 (8.7)
70-79	1693 (40.3)	612 (42.9)	575 (39.0)	506 (39.0)	808 (43.5)	524 (38.2)	361 (37.1)
80-89	1873 (44.6)	590 (41.3)	669 (45.3)	613 (47.2)	760 (40.9)	638 (46.5)	473 (48.8)
≥90	169 (4.0)	37 (2.6)	58 (3.9)	74 (5.7)	49 (2.6)	67 (4.9)	53 (5.4)
<b>Race-ethnicity</b>							
White	2083 (49.5)	662 (46.4)	798 (54.1)	622 (47.9)	856 (46.1)	740 (53.9)	487 (50.0)
Black	1405 (33.4)	505 (35.4)	424 (28.7)	476 (36.6)	675 (36.3)	393 (28.6)	337 (34.6)
Hispanic	716 (17.0)	261 (18.3)	254 (17.2)	201 (15.5)	326 (17.6)	240 (17.5)	150 (15.4)
<b>Education</b>							
High school or less	841 (20.0)	279 (19.6)	268 (18.3)	293 (22.8)	365 (19.8)	263 (19.3)	213 (22.0)
Some college	1646 (39.2)	521 (36.6)	609 (41.5)	516 (40.1)	704 (38.1)	549 (40.2)	393 (40.7)
College graduate	1693 (40.3)	625 (43.9)	590 (40.2)	478 (37.1)	779 (42.2)	554 (40.6)	360 (37.3)
<b>Health Characteristics</b>							
<b>Physical Activity (mins/day)</b>	344.2 (98.4)	374.8 ± 102.8	346.9 ± 88.4	307.5 ± 92	373.4 ± 99.1	338.6 ± 87.8	296.3 ± 90.9
<b>Sleep Disturbances</b>	6.27 ± 4.48	5.8 ± 4.4	6.3 ± 4.4	6.7 ± 4.6	6.0 ± 4.4	6.3 ± 4.4	6.8 ± 4.7
<b>BMI (Kg/m<sup>2</sup>)</b>	28.0 ± 5.7	28.1 ± 5.7	27.8 ± 5.5	28.3 ± 6.0	28.3 ± 5.8	27.7 ± 5.5	28.0 ± 5.8
<b>Physical Functioning (0-100)</b>	69.6 ± 25.7	72.8 ± 24.5	72.0 ± 24.0	63.2 ± 27.7	72.0 ± 24.8	71.1 ± 24.3	62.7 ± 28.1
<b>Comorbidity Index (≥2 conditions)</b>	584 (13.9)	170 (11.9)	211 (14.3)	203 (15.6)	228 (12.3)	191 (13.9)	165 (16.9)
<b>Depression Score (0-1)</b>	0.03 ± 0.1	0.03 ± 0.1	0.02 ± 0.1	0.03 ± 0.1	0.03 ± 0.1	0.02 ± 0.1	0.03 ± 0.1
<b>Self-rated Health</b>							
Excellent	2154 (51.2)	786 (55.2)	805 (54.7)	563 (43.5)	997 (53.9)	730 (53.3)	427 (44.1)
Good	1666 (39.6)	552 (38.8)	554 (37.7)	560 (43.3)	736 (39.8)	519 (37.9)	411 (42.4)
Poor	369 (8.8)	86 (6.0)	112 (7.6)	170 (13.1)	118 (6.4)	120 (8.8)	131 (13.5)
<b>Current smoker</b>	101 (2.4)	46 (3.2)	22 (1.5)	33 (2.5)	54 (2.9)	26 (1.9)	21 (2.2)
<b>Reynolds Risk Score<sup>1</sup></b>	12.3 ± 10.6	11.3 ± 10.0	11.8 ± 10.1	14.0 ± 11.7	11.5 ± 9.8	12.2 ± 10.4	14.0 ± 12.1

**Table 3.2:** HRs for log-based and accelerometer measured sleep duration and incident CVD

Sleep Duration Category	Median Sleep Duration (hours/night)	Model 1 HR (95% CI) <sup>a</sup>	Model 2 HR (95% CI) <sup>b</sup>	Model 3 HR (95% CI) <sup>c</sup>	Model 4 HR (95% CI) <sup>d</sup>
<b>Log-based sleep duration</b>					
<b>8-9 hours</b>	8.47	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
<b>short sleep (&lt;8 hours)</b>	7.40	1.07 (0.84, 1.37)	1.07 (0.84, 1.37)	1.08 (0.85,1.38)	1.12 (0.88, 1.43)
<b>long sleep (&gt;9 hours)</b>	9.65	<b>1.27</b> <b>(1.01-1.61)</b>	<b>1.27</b> <b>(1.01-1.61)</b>	1.13 (0.89,1.43)	1.05 (0.83, 1.34)
<b>Accelerometer sleep duration</b>					
<b>8-9 hours</b>	8.44	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
<b>short sleep (&lt;8 hours)</b>	7.29	1.06 (0.85, 1.33)	1.05 (0.84, 1.32)	1.07 (0.85, 1.34)	1.13 (0.90, 1.42)
<b>long sleep (&gt;9 hours)</b>	9.60	1.08 (0.84, 1.40)	1.07 (0.83, 1.39)	0.95 (0.73, 1.23)	0.87 (0.67, 1.13)

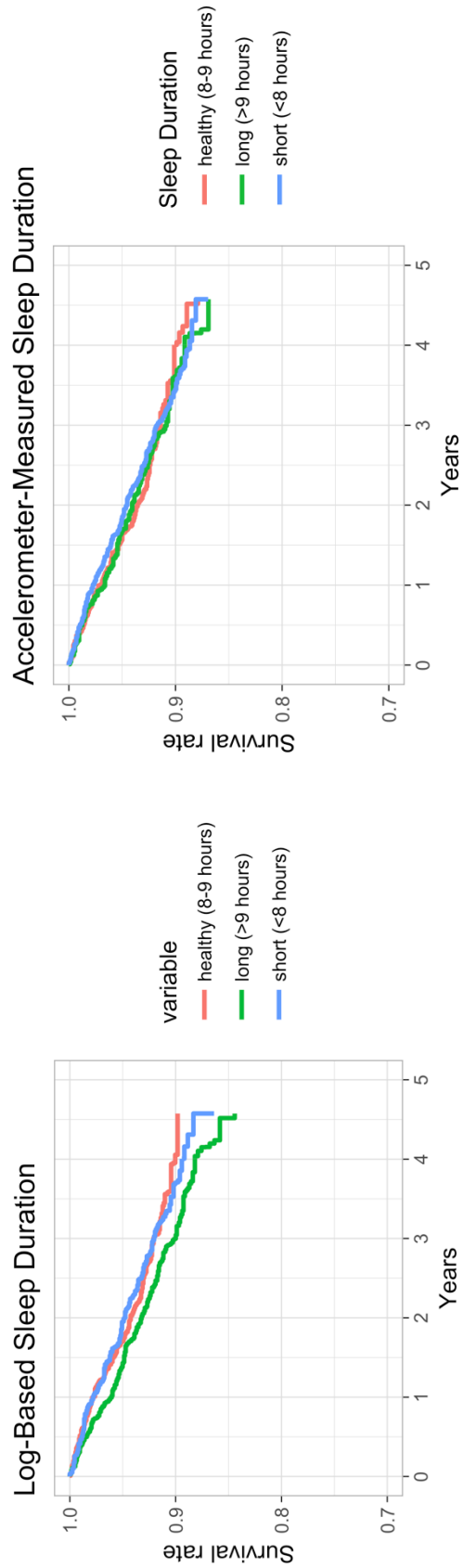
Ref, reference category

<sup>a</sup> Model 1 adjusted for race/ethnicity and age

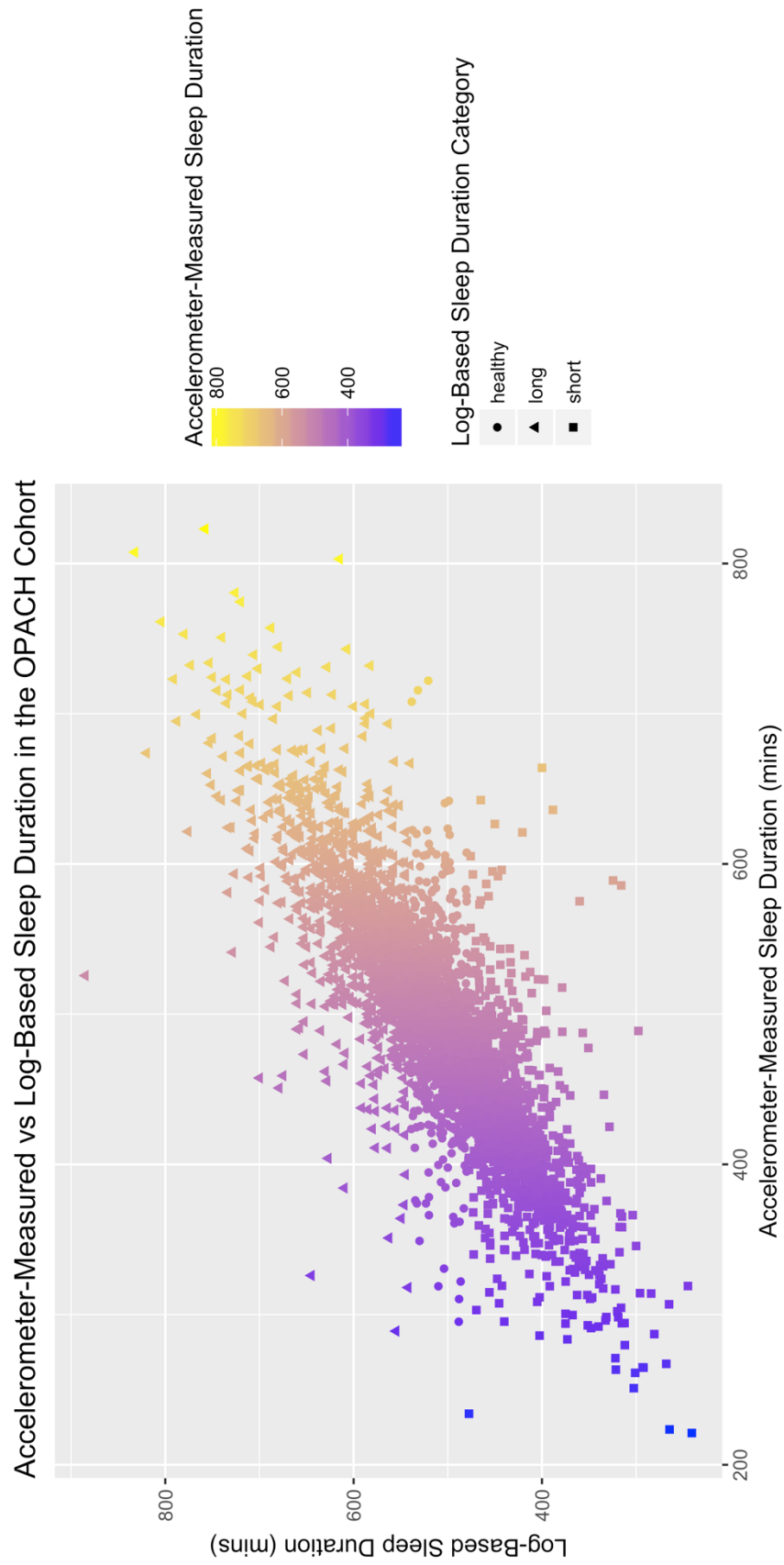
<sup>b</sup> Model 2 adjusted for race/ethnicity, age, education, and smoking

<sup>c</sup> Model 3 adjusted for race/ethnicity, age, education, smoking, comorbid conditions, physical functioning, and self-rated health

<sup>d</sup> Model 4 adjusted for race/ethnicity, age, education, smoking, physical functioning, comorbid conditions, self-rated health, and total minutes of PA



**Figure 3.1:** Adjusted survival curves for incident CVD by sleep duration category.



**Figure 3.2:** Accelerometer-measured vs. log-based sleep duration in the OPACH cohort.

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## DISCUSSION

Cardiovascular Disease (CVD) is the most prevalent chronic disease in the aging population.<sup>1</sup> Despite the overall reduction in deaths in the last two decades, CVD is still a significant public health problem, especially for women. There is growing evidence supporting sleep duration as a risk factor for CVD in older women, however there remains gaps in the literature. This dissertation was designed to build upon and advance the existing research on sleep and cardiovascular health in older women. Employing accelerometer-measured sleep duration collected in a large and diverse cohort of older women, this dissertation contributes new scientific evidence with more accurate measurement in new population groups. In this dissertation, accelerometer-measured sleep duration was examined in relationship to markers of cardiometabolic health, 10-year estimated risk of CVD, and CVD events. This comprehensive approach advances the understanding of the role that sleep duration plays in the development of CVD.

Three overarching themes emerged from this work. (1) There is a clear non-linear relationship between sleep duration and cardiometabolic outcomes which has not been thoroughly examined previously. Both short and long sleep durations were associated with higher values of several cardiometabolic markers and with higher 10-year estimated CVD risk. (2) In older women, there is a difference between log-based self-reported and accelerometer-measured sleep duration. It appears that self-reported sleep duration may be a measure of overall health status, calling into question previous evidence. (3) When examining sleep and cardiometabolic health, it is important to consider the interrelationship of sleep and other behaviors in the 24-hour day; most previous CVD studies in adults have not included sleep in analyses.

### ***Sleep Duration and Associations with Cardiovascular Risk Factors***

Chapter 1, entitled *Modeling the cardiometabolic benefits of sleep in older women: exploring the 24-hour day*, assessed the independent associations of accelerometer-measured sleep duration and markers of cardiometabolic health. In the series of cross-sectional analyses, the relationship between sleep and cardiometabolic outcomes appeared to differ across different markers, with a linear relationship for insulin, HOMA-IR, total cholesterol, and triglycerides and a u-shaped relationship with CRP, glucose, and waist circumference. This analysis included adjustment for age, race/ethnicity, and known covariates. These study results are consistent with previous single behavior analyses and meta-analyses demonstrating that accelerometer-measured sleep duration is related to several markers of cardiometabolic health including measures of metabolic function, gluco-regulatory function, and systemic inflammation.<sup>2-5</sup> Of note, in our sample there was no significant relationship found between sleep duration and BMI. Previous results have been mixed on the relationship between sleep duration and BMI, with some studies suggesting a u-shaped relationship and others finding no significant association.<sup>6-8</sup> Previous authors have suggested conflicting results may be due to differences in the ages of samples, which may also explain the difference found in the results in this cohort.<sup>2</sup> While we did not find a relationship between sleep duration and BMI, there was a significant non-linear relationship between sleep duration and waist circumference in our sample, which is another measure of body composition. Additionally, the relationship between sleep duration and systolic blood pressure was not significant in our analysis. Previous studies have found a significant relationship between sleep duration and hypertension, however it has been suggested that this relationship may be modified by age, which may explain why we did not find a significant

association in this sample of older women.<sup>2,5,9,10</sup> Further, many women in this sample are already medicated for hypertension and therefore it is difficult to adequately explore this relationship. By including a range of cardiometabolic markers and accelerometer-measured sleep duration from a large cohort of older women, these analyses provide a more comprehensive view of the relationship between sleep duration and cardiometabolic health in older women than has been previously examined. Additionally, this is one of the first studies to provide evidence of the U-shaped relationship between sleep duration and cardiometabolic markers in older women using accelerometer-measured sleep duration.

While examining CVD risk factors individually with cross-sectional analyses may explain the immediate relationship between sleep and cardiometabolic health it may not explain the relationship between sleep and overall CVD risk. Chapter 2 - *Association between accelerometer-measured sleep duration and clinical cardiovascular risk factor scores in older women* - built on the analyses in Chapter 1 and demonstrated that sleep duration was non-linearly associated with 10-year estimated CVD risk among older women. The chapter details how both short and long sleep duration was associated with higher 10-year CVD risk, estimated by a clinically relevant composite risk score, and the shape of the relationship was explored. After several adjustments, the non-linear shape persisted. This study is one of the largest studies to provide additional evidence that sleep duration, measured with accelerometry, is non-linearly associated with a measure of CVD risk in older women. To our knowledge this study provides new evidence on the shape of the relationship between sleep duration and estimated CVD risk, with the use of accelerometry and a clinically relevant risk factor score.

### ***Sleep Duration and Incident CVD***

To advance the scientific field and determine if sleep duration is a risk factor for CVD, prospective studies that relate sensor-measured sleep duration with the incidence of CVD events are needed to clarify and build upon previous findings. In Chapter 3, *Accelerometer-measured sleep duration and cardiovascular incidence in post-menopausal older women: Evidence from the Women's Health Initiative* the relationship between cardiovascular events over 3-5 years of follow-up and sleep duration was examined. This is one of the first prospective studies to examine the association between accelerometer-measured sleep duration and incident CVD in older women. The chapter details that neither short nor long sleep duration was associated with an increased risk of CVD over the 3 to 5-year period. These results were consistent between both log-based sleep duration and accelerometer-measured sleep duration, across several categories of short and long sleep duration. In addition to filling the gap in the evidence, this chapter provides further examination of the differences between a measure of self-reported sleep duration and accelerometer-measured sleep duration. Exploratory models found that the difference in sleep duration estimates was significantly related to the participant's physical functioning scores and total minutes of physical activity (PA). This difference in self-reported sleep duration, and the longer sleep durations reported by women, when compared to accelerometer estimates, may be a reflection of the women's overall health status, including both physical and mental health, and not necessarily reflective of their sleep. The findings of this chapter suggest that sleep duration may not be an independent risk factor for CVD. The previous longitudinal studies that found sleep duration, short or long, was independently associated with an increased risk of CVD events and CVD mortality were all based on self-reported estimates of sleep duration.<sup>11-19</sup> The differences found between log-based and accelerometer-measured sleep duration in our sample proposes doubt in the previous evidence based on self-report. To our knowledge, there have been

no studies that have shown sleep duration, measured with accelerometry or actigraphy, is an independent risk factor for CVD. The results of this chapter support the need for future studies that include multiple time points of sleep duration, measured either by polysomnography or actigraphy, as well as the assessment of sleep disorders, to adequately explore the relationship between sleep duration and CVD risk in older women.

### ***Sleep Duration and the 24-Hour Day***

In this dissertation, we learned that sleep duration was related to markers of cardiometabolic health and intermediate CVD risk, but that sleep duration did not independently predict incident CVD. These findings may be explained by the interdependence of 24-hour activities, including sleep duration, PA and sedentary behavior, and their relationship to cardiometabolic health. This consideration of 24-hour activity is an important step in advancing the science and the understanding of the relationship between sleep duration and CVD.

This dissertation provides evidence that accelerometer-measured sleep duration is related to cardiometabolic health. We also know that sedentary behavior (SB) and PA, two other behaviors that make up the 24-hour day, are related to cardiometabolic health. Emerging evidence also demonstrates that sleep is related to these other behaviors that are associated with CVD risk.<sup>20</sup> Within the OPACH cohort, previous analyses have found that light PA (LIPA) was protective against incident CVD, and higher levels of SB were associated with increased risk of incident CVD.<sup>21,22</sup> These various analyses in the OPACH cohort provide evidence of how 24-hour activities are interrelated. This dissertation is consistent with previous research demonstrating that sleep duration is associated with daily PA and SB, which are related to CVD risk.<sup>23-25</sup> Moving forward, we must consider that, even after statistical adjustments, 24-hour activities are not independently related to cardiometabolic health and CVD risk. While we can

continue to study these behaviors in isolation, it will be difficult to untangle the interrelated effects they have on cardiometabolic health. The 24-hour day is comprised of a combination of activities that are both harmful and beneficial to cardiometabolic health. Each additional minute of MVPA is good for our health. Each additional hour of SB is bad for our health. Increasing or decreasing time spent in one behavior results in an increase or decrease in time spent in another behavior. All of these daily activities are bounded by the 24-hour day.<sup>26-28</sup> Therefore, the behaviors throughout the 24-hour day are interdependent, and we must take this into consideration when we examine their relation to cardiometabolic health. In Chapter 1, the isotemporal substitution analysis was one method to assess the interrelationships of 24-hour activities. The chapter explored the use of the isotemporal models to examine the associated change in cardiometabolic risk of reallocating time spent sleeping; shifted to or from LIPA, moderate to vigorous PA (MVPA), or SB. While isotemporal modeling is not new, this is one of the first studies to use the approach with accelerometer-measured sleep duration and take into account the U-shaped relationship between sleep duration and cardiometabolic health. Our study results show that in long sleepers when time was reallocated from sleep to MVPA or LIPA it was associated with favorable cardiometabolic maker values. Further, when time was reallocated from SB to sleep in short sleepers it had beneficial associations with several cardiometabolic markers. This chapter suggests that cardiovascular interventions for older women should continue to target increasing LIPA and MVPA and reducing SB, but should also consider the role of sleep duration. For example, more time in bed not sleeping may not be beneficial, but reducing sleep time to add exercise in the morning could be advantageous. While the results of this dissertation do not support sleep duration as a risk factor for CVD, they do support sleep duration as a lifestyle behavior worth targeting for cardiometabolic risk reduction.



## **FUTURE DIRECTIONS**

The composition of the day matters and activities throughout the 24-hour day are interdependent. Rather than continuing to examine LIPA, MVPA, SB, and sleep as independent and mutually exclusive categories, it may be worthwhile to shift our focus from individual behavior goals, to understanding 24-hour behavior profiles. Is there a composition of time spent in LIPA, MVPA, SB, and sleep that increases or decreases a women's risk of CVD? The disparities in the high incidence and prevalence of CVD and CVD risk factors in groups of women highlight that current prevention strategies are not effective for these populations; there may be alternative combinations that are more feasible and effective. The majority of current CVD lifestyle interventions have targeted changing one behavior without considering the impact this will have on the other behaviors that make up the 24-hour day, including sleep. It is important we move beyond the paradigm of considering activities in isolation. It is exciting to think about the intervention design opportunities that come with changing our focus to 24-hour behavior profiles. We can design future cardiovascular lifestyle interventions with multiple behavior targets, including more specific activity replacement targets, or sequential behavior targets that include all 24-hour activities. Most importantly these interventions can be tailored, with behavior targets that are not only more feasible for older women, but may have greater benefits for their cardiometabolic health. While these interventions may be complex, this dissertation supports that sleep behavior is complex, as is each of the other activities throughout the 24-hour day. It does not serve us to continue to consider these 24-hour activities, including sleep, in isolation. Complex behaviors deserve more complex and thoughtful approaches to behavior change.

Beyond expanding our thinking to develop new study designs and data collection methods that consider 24-hour assessment, we must also employ statistical methods and a larger framework that consider the composition of the 24-hour day in its relationship to health. In the current field of Public Health, sleep researchers, PA researchers, and SB researchers are often separate and conducting research independently. A 24-hour framework calls for the dilution of the boundaries of these behavior domains and a more integrative team science approach. A more integrative approach may be just what is needed to address the public health issue of CVD in older women.

More generally than just applying this new 24-hour paradigm to CVD research, we need to consider that the ideal 24-hour day for optimal heart health, may not be optimal for other outcomes, including mental health, cancer prevention, or weight loss. Recently, researchers from different international institutions, including myself and representatives from UCSD, attended a workshop at the University of Auckland to discuss approaches to 24-hour data. The workshop brought together experts in accelerometry, 24-hour measurement, time-use epidemiology analysis, and behavioral interventions with the intention of forging a path forward to advance the science of 24-hour activity and improve activity behavior guidelines. Results from 24-hour compositional analyses are starting to demonstrate that the ideal 24-hour day for the optimal cardiometabolic health of women looks very different than the 24-hour day that results in the best mental health outcomes for women. The more we employ a 24-hour approach to study design, data collection, and interventions the more we will learn that the 24-hour day matters, for every health outcome.

The 24-hour concept is ideal and will be a challenge to pursue. Currently, there are many challenges from data collection to data analysis. For measurement of the 24-hour day, in most

cases the location of sensor still depends on the primary outcome behavior. Wrist accelerometers are considered the best location for sleep duration and quality,<sup>29,30</sup> but data processing methods are still under-developed for the assessment of MVPA and SB. The number and popularity of consumer wearables may be contributing to the increase in 24-hour data assessment, but may be also contributing to the challenges in 24-hour research. As the number of devices being used for research continues to increase so does the difficulty in drawing conclusions across studies. In addition, compliance over the 24-hour day across multiple days is a challenge and will remain a challenge. In this dissertation, of the 6489 women with accelerometer data only 68% of participants had valid night wear with >2 nights of data. In addition, best practice for the processing of sleep data from sensors still includes large resources, such as visual scoring of the data before the application of algorithms. For this dissertation, the visual scoring of each participant file took approximately 15 minutes. When this is scaled to large a cohort study, this accumulates to a significant amount of person-hours for research teams. At present, that best practice data processing techniques are different for PA, SB, and sleep. To be mindful in getting the best estimates of each activity and then aggregating the data takes a significant amount of work. Further, there is still a gap in the understanding of the best ways to approach 24-hour day analysis conceptually. For activities during the waking day we consider a 24-hour day as 12 am to 12 am. For sleep, this approach would cut the night of sleep in half. Should the 24-hour day then be in-bed time to in-bed time? What if bed time varies greatly within an individual, how do we account for that variation? Lastly, while the composition of activity throughout the 24-hour day is important, current compositional analysis approaches do not account for patterns in activity that have been shown to be related to health, such as breaks in sitting,<sup>31</sup> bouts of PA,<sup>32</sup> or

number of night time awakenings.<sup>33</sup> Evidence suggests that these daily patterns in activity are uniquely related to health outcomes, and need to be incorporated in future 24-hour research.

## **LIMITATIONS**

This dissertation is not without limitations. The OPACH cohort, while a rich and unique dataset, includes only older women over the age of 63 years who have had no previous incidence of CVD, and therefore is not generalizable to the population as a whole. These women make up a unique subpopulation who are at increased risk for CVD, but who have also survived (mean age of 78.5 years) without experiencing a previous CVD event. It is possible that many of our findings are not generalizable to other population groups. Our primary exposure, sleep duration, was only assessed at one time point, and therefore we were not able to explore fully the relationship between sleep duration and the development of poorer health that some of our results suggest. It is possible that many of our findings are based on the current cardiometabolic health of women that has developed over time, and one assessment of sleep does not allow for us to examine the role that sleep duration played in the development of the poorer cardiometabolic health of some women in the cohort. Further, while accelerometry provides better estimates of sleep duration than self-report, accelerometers on the hip have shown to provide longer estimates of sleep duration when compared to polysomnography and wrist actigraphy.<sup>29</sup> Because we employed hip accelerometers, valid for total sleep duration only, we were not able to examine aspects of sleep quality, beyond self-reported sleep quality. Although unclear, we suspect that the compliance issue we had with over 30% of our sample not wearing the device at night may be due to the hip location of the accelerometer. Women may have found that the device was

difficult to sleep with. The issue with 24-hour compliance in this cohort did significantly limit our sample size, which may explain the smaller proportion of short sleepers in our sample, which was unexpected. Lastly, sleep disorders, such as obstructive sleep apnea (OSA) was not included in our analyses, as they were not assessed in the LLS questionnaire. Previous research suggests that sleep disordered breathing and OSA are risk factors for CVD,<sup>34,35</sup> and possible confounders in the relationship between sleep duration and CVD.<sup>3</sup>

## **CONCLUSIONS**

In summary, sleep is essential to well-being. There has been research supporting this fact for decades and the evidence continues to grow. This dissertation provides further support that sleep duration, measured with an accelerometer, is associated with cardiometabolic health in older women. As we continue to examine sleep duration in relation to cardiometabolic health, it is important that we do so within the framework of the 24-hour day. To better understand how sleep relates to cardiometabolic health, we must better understand the interdependence and interrelationships of activities throughout the 24-hour day. Further we need to pay attention to short and long sleepers as there is evidence to support that both ends of the U-shaped curve have poorer cardiometabolic health. With the increasing prevalence of CVD in the aging population, and the need for novel CVD prevention and intervention strategies it is important to consider a compositional approach to examining the relationship between the activity throughout the 24-hour day and cardiometabolic health. Advancing research to consider the composition of the 24-hour day will better inform the optimal proportion of time spent in sleep, PA, and SB needed for optimal cardiovascular health.

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