Sleep-related Mediators of the Physical Activity and Sedentary Behavior-Cardiometabolic Biomarker Relationship in Middle Age Adults

by

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ABSTRACT

Physical activity, sedentary behaviors, and sleep are often associated with cardiometabolic biomarkers commonly found in metabolic syndrome. These relationships are well studied, and yet there are still questions on how each activity may affect cardiometabolic biomarkers. The objective of this study was to examine data from the BeWell24 studies to evaluate the relationship between objectively measured physical activity and sedentary behaviors and cardiometabolic biomarkers in middle age adults, while also determining if sleep quality and duration mediates this relationship. A group of inactive participants (N = 29, age = 52.1 ± 8.1 years, 38% female) with increased risk for cardiometabolic disease were recruited to participate in BeWell24, a trial testing the impact of a lifestyle-based, multicomponent smartphone application targeting sleep, sedentary, and more active behaviors. During baseline, interim (4 weeks), and posttest visits (8 weeks), biomarker measurements were collected for weight (kg), waist circumference (cm), glucose (mg/dl), insulin (uU/ml), lipids (mg/dl), diastolic and systolic blood pressures (mm Hg), and C reactive protein (mg/L). Participants wore validated wrist and thigh sensors for one week intervals at each time point to measure sedentary behavior, physical activity, and sleep outcomes. Long bouts of sitting time (>30 min) significantly affected triglycerides (beta = .15 (±.07), $p<.03$); however, no significant mediation effects for sleep quality or duration were present. No other direct effects were observed between physical activity measurements and cardiometabolic biomarkers. The findings of this study suggest that reductions in long bouts of sitting

time may support reductions in triglycerides, yet these effects were not mediated by sleep-related improvements.

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CHAPTER 1

INTRODUCTION

Physical activity and sleep are widely considered necessities for good physical and mental health. However, over half of Americans report getting less sleep on work nights than needed.[1] More concerning is the estimation by the CDC that 50 – 70 million Americans that have sleep disturbances, which is a disorder of sleep or wakefulness.[2] Physical activity has been suggested to have a positive correlation to sleep quality and duration in previous studies.[3] It is discouraging that only 21% of U.S. adults are meeting the overall physical activity recommendations of 150 minutes of moderate-intensity aerobic activity per week and two days per week of muscle-strengthening activities.[4,5] There are numerous sleep disturbances that can interrupt the sleep cycle.[6] Some biomarkers (e.g., cholesterol, C – reactive protein, and HbA1c) in persons with sleep disturbances have been shown to vary outside of levels that are considered healthy.[7 - 9] That being said, few studies have determined whether or not sleep can act as a mechanism to explain the relationship between physical activity and cardiometabolic biomarkers.

Evidence suggests that physical activity can improve sleep quality by means of improving body temperature regulation, decreasing stress, raising physical fatigue levels, and keeping the circadian rhythm regulated.[10] Physical activity has also been shown to have positive effects on biomarkers such as blood lipids, C-reactive protein (CRP), blood pressure, blood glucose levels, and insulin levels.[11 – 13] Some studies have prospectively linked sleep disturbances to certain biomarker abnormalities (e.g. glucose, insulin, blood

lipids) ,[14, 15] while other research has shown reverse linkages suggesting biomarker abnormalities driving marked sleep disturbances.[16, 17]

Evidence suggests that physical activity has a dose-response relationship to cardiometabolic biomarkers.[18] There is also evidence suggesting that physical activity is positively associated with sleep duration, with the strongest directional evidence suggesting regular physical activity improves sleep quality.[3] It is unclear whether the influence of physical activity on cardiometabolic health may be at least partially explained by the impact physical activity may have on sleep. This creates the need to determine if physical activity independently influences cardiometabolic biomarkers, or if the effects on these biomarkers are mediated by improvements in sleep. Identifying the role that sleep may play in the current relationship between physical activity and cardiometabolic biomarkers will be useful for future recommendations on methods to improve cardiometabolic outcomes through a possible sleep health pathway.

To examine these relationships, a prospective secondary data analysis of a pilot, 8-week, clinical trial testing the effects of a smartphone-based "app" targeting sleep, sedentary, and physical activity behaviors in a sample of mid-life men and women with elevated risk for cardiometabolic diseases was conducted. Specifically, the study was to determine whether the associated changes in cardiometabolic parameters accounted for by improvements in physical activity may be mediated by improvements in sleep duration and quality.

Purpose:

There were two aims of this study: 1) to examine the relationship between 8-week changes in objectively measured physical activity and cardiometabolic biomarkers in middle age adults age 35-65 y and 2) to determine whether sleep duration and quality acted as a mediator of this relationship.

H1: Changes in physical activity will show a positive association with cardiometabolic biomarkers in middle age adults.

H2: Sleep duration and quality will partially mediate the relationship between changes in physical activity and cardiometabolic biomarkers in middle age adults.

Definitions:

Sleep disturbance: a disorder of starting or stopping sleep, a disorder of excessive drowsiness, a disorder of the sleep-wake schedule, and any abnormality of sleep, the stages of sleep, or arousals during sleep[6]

Biomarker: an objective measurement of almost any biological system[19]

Mediator: a variable that can explain the relationship between the independent and dependent variables

Blood lipids: includes measurements of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides

C-reactive protein: a substance that comes from inflammation and can lead to cardiovascular disease

Circadian rhythm: physical, mental, and behavioral changes that align themselves with a 24-hour daily cycle[20]

BMI: weight in kilograms divided by the square of height in meters

Limitations:

Limitations of this study include a possible response bias because the participants were aware of the accelerometers and what they measured. The sample size of BeWell24 was also small, limiting the statistical power to identify mediating relationships.

Delimitations:

Delimitations of this study include the recruitment of participants from specific locations. Participants were recruited at the Phoenix VA Health Care System and Arizona State University. This may not be a representative population because of the limited recruitment locations.

CHAPTER 2

REVIEW OF LITERATURE

Physical Inactivity Prevalence:

Global physical inactivity is estimated to be at least 31.1% and data also suggest that over 33% of adults do not meet physical activity recommendations.[21] The amount of adolescents not meeting physical activity recommendations has reached 80%[22] The goal of the World Health Organization (WHO) and it's member states is to reduce global physical inactivity by 10% by 2025, yet only 56% of member states in the WHO have policies aimed at reducing physical inactivity.[22] Estimates from the WHO put the increased risk of mortality for a physically inactive individual at 20% to 30%. The WHO lists physical inactivity as the fourth leading risk factor for mortality in the world.[22]

Effects of Physical Inactivity:

The impact of physical inactivity on a global health and economic level is immense. Kohl et al. report that there is evidence linking physical inactivity to 6-10% of all deaths not related to communicable diseases.[21] 2007 alone saw at least 5.3 million deaths from non-communicable diseases that could have potentially been prevented if inactive individuals were active instead.[21] Also, the direct health care costs per head associated with physical inactivity is estimated to be $28.4 - $334.4 in Australia, the UK, and even Switzerland.[21] This number inflates to $154.7 - $418.9 in the U.S.[21]

Lee et al. examined physical inactivity even further and sought to quantify the link between physical inactivity and life expectancy by examining population attributable fractions associated with physical inactivity.[23] The authors estimate that physical inactivity causes 7% of type 2 diabetes, 10% of breast cancer, and 10% of colon cancer.[23] If the WHO is successful in reducing global physical inactivity by just 10%, Lee et al. believe that over 500,000 death can be prevented each year.[23] They also suggest that the complete elimination of physical inactivity in the world would increase global life expectancy by .68 years.[23] It is clear that physical inactivity is a global health concern and no population is unaffected. Poor sleep is also a problem that appears to afflict populations on an international scale.

Sleep Health:

There are many known influences on sleep, some are even classified as disorders. Defining exactly what a sleep disorder is and how poor sleep affects individuals will establish the importance of this study. Also, knowing what the current sleep recommendations are for adults is crucial to understanding the magnitude of any issue that may be present in this study population. Fortunately, the US government utilizes tools such as the nationwide NHANES survey to create such recommendations.

Wheaton et al[24] conducted a study of the 2005-2006 and 2007-2008 NHANES data for the CDC to determine the effects of insufficient sleep on daily activities in adults. The amount of respondents included in this report was 10,896. Participants were split into age groups of 20-39 y, 40-59 y, and >60 y.[24] Less than 7 hours of sleep per night was

considered a short sleep duration. It was reported that 37.1% of respondents stated that they slept for <7 hours per night.[24] In adults who reported that they had <7 hours of sleep per day, the prevalence of all reported sleep difficulties was higher than respondents who reported 7-9 hours of sleep per day.[24] A major limitation of this report is that the data are from self-report. Also, NHANES is cross-sectional and cannot show a causal relationship between sleep duration and sleep related difficulties.[24] Results of this study suggest that there is a significant association between sleep duration and sleep reported difficulties in adults. The authors make note that over a third of the U.S. population does not get over 7 hours of sleep and may experience difficulty performing daily tasks.[24]

Sleep Duration:

Short sleep duration is widely recognized as sleep that is less than six hours. Luckhaupt et al. examined the prevalence of self-reported sleep duration among civilian employed workers in the U.S. to determine if the prevalence has increased by using the National Health Interview Survey from 1985, 1990, and 2004-2007.[25] A sample of 74,734 adults in a combination of surveys from 1985 and 1990 reported a short sleep prevalence of 24.2%, while a sample of 110,422 adults between 2005 and 2007 reported 29.9%.[25] This data suggest that the prevalence of short sleep among civilian workers increased 5.7% in under 20 years.

Bin et al. examined the prevalence of short and long sleep duration (>9hrs) in 10 countries.[26] Despite numerous studies suggesting the increase of short sleep durations around the world, Bin et al. actually report that their data suggest a decrease in short sleep

between the 1970s and the 2000s in the United States, United Kingdom, Finland, and Sweden.[26] However, short sleep duration did increase in Italy, and Norway.[26] The authors report an increase of long sleep duration in Australia, Finland, Sweden, United Kingdom, and the United States.[26] Long sleep duration has many negative health influences along with short sleep duration.[26] A possible explanation for these data, according to the authors, is that the definition of sleep used in the study was time in bed, resting periods, and napping.[26] These definitions of sleep disregard sleep disturbances that can significantly alter actual sleep times. A validated method of sleep measurement to control for sleep disturbances and measure actual time asleep is to use wearable sensors. Nonetheless, these data show an evolving picture of sleep duration that has not improved over the past few decades.

Sleep Quality:

There are numerous types of sleep disorders that can alter a normal night of sleep for adults. In order to target efforts of sleep improvement it is important to study the prevalence of sleep disorders in adults. According to Fetveit et al[27], insomnia has a 10 – 50% estimated prevalence in adults. Insomnia is related to having a hard time falling asleep, staying asleep, and waking up too early.[27]

Demir et al[28] conducted a study to determine the prevalence of sleep disorders in Turkey. There were a total of 5,021 participants ages 18 to 90 years (mean 40.7 ± 15.1) in this study.[28] The authors used a questionnaire to gather sleep data from participants that included a total of 132 questions.[28] Sleep disorders in this population were defined using

previously established tools. These tools include the International Restless Legs Syndrome Study Group Criteria for restless leg syndrome, the DSM-IV Criteria for insomnia, the Berlin Questionnaire for risk of sleep related breathing disorders and snoring, and the Epworth Sleepiness Scale for excessive daytime sleepiness.[28] The prevalence of the risk of sleep related breathing disorders was 13.7%, restless leg syndrome was 5.2%, snoring was 9.6%, and excessive daytime sleepiness was 5.4%.[28] A limitation of this study was the self-report data of the questionnaires. Demir et al[28] report that data from this study suggest that different types of sleep disorders affect a large percentage of Turkish adults, despite being closely aligned with lower estimates of prevalence estimations in previous studies.

Sedentary Behavior

According to Proper et al., it is important to note that sedentary behavior is a different concept than physical inactivity.[29] Sedentary behavior includes activities performed while sitting or lying that do not increase energy expenditure considerably above the inactive level of 1.5 METs.[29] The United States Department of Agriculture (USDA) reports that roughly 67.5% of adults age 19 an older reported watching television for an average of at least two hours per day for the past 30 days.[30] It was also reported that 25.2% of adults used a computer outside of work or played computer games for at least two hours or more per day for the past 30 days.[30] Similar results can be found in Spain, China, and the Czech Republic.[31-33]

Numerous chronic conditions and mortality are associated with prolonged exposure to sedentary behaviors.[34] Ekelund et al. conducted a meta-analysis that included over one million individuals to determine if physical activity can eliminate the association between sitting time and mortality.[34] Sitting for more than eight hours per day and also having less than 2.5 MET-hours of physical activity per week increased the chance of death by 27% when compared to sitting for less than four hours.[34] TV viewing time of more than five hours per day and less than 2.5 MET-hours of physical activity per week increased the chance of death by 44% according to Ekelund et al.[34] In the group of TV viewers that watched TV for over five hours per day but also had over 35.5 MET-hours of physical activity per week, the increased risk reduced to 4%.[34] Those individuals that spent over eight hours per day sitting but still had 35.5 MET-hours of physical activity per week had a mortality risk of 15%, down from 44% in inactive group.[34] The authors also examined mortality from cardiovascular disease and cancer. Cancer mortality rates were 12-22% higher with more sitting time in the least active group that had less than 2.5 MET-hours of physical activity per week.[34] Mortality rates for cardiovascular disease were 23-74% higher in those who sat for four or less hours per day and had less than 2.5 MET-hours of physical activity per week than those who had more than 35.5 MET-hours per week.[34] The results from this study suggest that sitting and TV viewing are two sedentary behaviors that significantly increase mortality hazard ratios. These results also suggest that physical activity may drastically reduce or completely eliminate sitting and TV viewing mortality hazard ratios.[34]

Another meta-analysis was conducted by Chau et al. to study the association between daily sitting time and all-cause mortality.[35] Six studies that included 595,086 individuals were incorporated into the meta-analysis.[35] Chau et al. note that sitting time in the literature is suggested to be associated with an increased risk of cardiovascular disease, type 2 diabetes, cancer, and all-cause mortality.[35] The authors also report that sitting time accounts for 7% of deaths in individuals age 45 and older.[35] The results of this analysis suggest a 5% increase in all-cause mortality for every one hour increment of sitting time for adults sitting longer than seven hours per day.[35] The mortality results for individuals sitting less than seven hours were not as drastic, however the average of all studies included was 5.9%.[35]

Relationship between PA and Sleep:

If biomarkers are to have a mediating effect on the relationship between physical activity and sleep, that relationship should first be well-defined. Many investigations have examined this relationship and suggested similar results. Using these studies, it is possible to hypothesis what the results of this study may show and further focus on the influence of the biomarkers as mediators.

In an article posted in the American Journal of Lifestyle Medicine, Buman and King write that the low efficacy of pharmacological treatments for sleep disturbances is a reason that physical activity should be treated as a method to enhance sleep.[36] Buman and Kind also noted that moderate amounts of physical activity are acceptable to improve sleep quality according to the authors.[36] Additionally, the authors mention that physical

activity affects sleep through several health systems such as antidepression effects, restorative functions, and circadian effects.[36]

Physical activity has shown previous antidepressive effects which would suggest that physical activity may improve sleep due to depression contributing to lower sleep qualities and durations.[36] Buman and King make note that older adults are especially vulnerable to sleep disturbances and may see significant sleep improvements from increased physical activity.[36] Depression and anxiety often occur together and anxiety also has been linked to poor sleep, suggesting that physical activity may be effective at improving sleep duration and quality through similar pathways in each illness.[36] This information is vital to improving sleep outcomes as over 6.7% of adults in the U.S. alone will experience a depressive episode each year.[37]

During sleep, the body will release hormones to repair itself from the effects of daily activities. Buman and King suggest that there is evidence supporting the increased sleep quality and duration after daily exercise occurs due to the amplified energy expenditure.[36] The authors also report that exercise can mediate phase shifts of the circadian cycle, leading to an increased synchronization of circadian rhythms.[36] Buman and King present numerous studies that suggest many pathways for sleep duration and quality to be positively influenced by exercise of various durations and intensities.[36]

In a study by Irwin et al[38], the relationship between Tai Chi Chih and sleep was studied to determine if this method of physical activity can increase sleep quality in older adults. During this study, 189 individuals were assessed for eligibility and 102 participants enrolled (ages 59 – 86y) until the completion of the study. This study was a

randomized control trial (RCT) that consisted of one group assigned to Tai Chi Chih (N = 59), while another was assigned to health education (N = 53). The study lasted 25 weeks and the Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality in the participants. During the study, Tai Chi Chih sessions lasted for 40 minutes and were given to participants three times per week. Health education was also given to participants in an equal amount of time each week. Participants received Tai Chi Chih and health education for 16 weeks and then were followed up with nine weeks later. Data were gathered at baseline, 16 weeks, and then at 25 weeks. The data show that 63% of participants in the Tai Chi Chih intervention group were able to lower their PSQI scores below 5, while only 32% in the health education group lowered their PSQI below a 5. The authors report that limitations of this study are the sampling of older adults who have a higher social status and income, which could increase adherence rates.[38] Also, the measurement for sleep was not objective and could have produced results that may include those with unknown sleep disorders. The authors would have also liked to have a longer follow-up period as well.[38] Results of this study suggest that physical activity can improve sleep quality in older adults, even more so than health education.

Another study that examined the relationship between physical activity and sleep was reported by Tsunoda et al[10]. These researchers used a prospective cohort study design to determine if different intensities of physical activity could have an effect on sleep sufficiency. This study gathered data from health check-ups and though 16,267 check-ups were examined, 7,061 participants entered the study in a group reporting no short sleep duration and 7,385 entered in a group that was free of sleep insufficiency.[10]

Participants were also divided into two groups based on age. One group (n = 5,664) was <60 years (mean 45.7) and the other group (n = 1,721) was over 60 years (mean 65.3). The participants were followed for a mean of 3.4 years from baseline to follow-up. A national standard question was used to determine sleep sufficiency in participants and was validated using the PSQI. Sleep duration was measured by self-report survey and participants were asked to report their patterns of sleep duration in hours per day. Physical activity was also measured by a self-report survey and was split into intensities. The researchers used Cox proportional-hazards analysis to determine the extent of which physical activity was preventative of short sleep duration and insufficient sleep.[10] The hazard ratio for insufficient sleep in middle-aged adults who engaged in vigorous physical activity was .83 and for moderately high physical activity it was .81.[10] In older adults who engaged in moderately light physical activity the hazard ratio for insufficient sleep was .58.[10] The authors report that the study had limitations of using self-report data, having a much larger older population than middle-aged, and having a lack of socioeconomic variability.[10] Investigators in this study concluded that vigorous physical activity and moderately high physical activity in middle age adults and moderately light physical activity in older adults all have significant preventative influences on insufficient sleep.[10] However, there were no data suggesting a significant effect on sleep duration.[10]

Cardiometabolic Biomarkers - Relationship to PA:

Sleep may be a mediator in the relationship between PA and cardiometabolic biomarkers, but it is important to determine if PA and sleep are associated to any biomarkers exclusive of each other. By studying these associations, there is an opportunity to understand and explain any mediation that may be present in the results of this study.

In a study by Chien et al[12], the association of physical activity with blood pressure and blood glucose was examined. Data for this study was taken from the National Health and Morbidity Survey completed in 2011 in Malaysia. This survey collected data from 18,231 respondents with an average age of 42 (±16).[12] The International Physical Activity Questionnaire (IPAQ) was used to measure the overall physical activity of respondents in MET-minutes/week. Blood glucose was measured using a six hour fasted finger prick test. Simple and multivariable linear regression analyses suggested that physical had a significant dose response relationship with blood glucose.[12] The adjusted coefficient from low physical activity group was .17 and only .03 in the moderate physical activity group.[12] One limitation of this study was that it used self-reported data from the IPAQ to measure overall physical activity. The authors reported that because their study was cross-sectional and not a prospective cohort or randomized control trial (RCT), the results cannot be considered conclusive when determining a dose response relationship.[12] The results of this study suggest that physical activity may directly influence blood glucose levels in adults.

Mainous et al. also studied the effects of physical activity on glucose levels in 1,153 healthy weight adults from the 2014 Health Survey for England.[39] The population included in this study was over the age of 20 and had a BMI between 18.5 and 24.9.[39] The authors reported that abnormal glucose levels were found in 23.7% of participants who had low activity levels, 14.8% in ones that had medium levels, and in 12.2% in low levels of physical activity.[39] An interesting note is that inactive individuals were 25.4% more likely to have abnormal glucose levels than inactive individuals.[39] The strengths of this study were that the data were nationally represented and it was from healthy individuals instead of those with a history of abnormal glucose levels. As for limitations, the investigators made note that the data were from self-report (IPAQ) and they did not account for diet and family history.[39] Furthermore, this study was cross-sectional, which can be seen as a limitation due to no measure occurring over time. The data from Mainous et al. suggest that a higher level of physical activity is significantly associated with lower glucose abnormalities.[39]

One of the reasons that physical activity may influence blood glucose levels is the effect it has on insulin, which regulates glucose levels in the blood. A RCT was conducted by Andersen et al. to study the effects of a five month physical activity intervention on glucose and serum insulin levels in Pakistani immigrant men in Oslo, Norway.[40] A total of 150 men were randomized for the study. The intervention group had 89 men with a mean age of 35.7 (6.1) and the control group had 61 men with a mean age of 39.7 (9.2).[40] Out of the included men, 76 completed the post-test in the intervention group and 50 in the control group. Data were collected on physical activity habits and

risk factors for diabetes before and after the intervention. Physical activity was objectively measured during the intervention with an ActiGraph accelerometer. Participants wore these accelerometers for seven days on the right hip. Twelve hour fasted blood draws and oral glucose tolerance tests were completed before and after the intervention.[40] The investigators reported that the intervention group increased their PA levels by 15% more than the control group and also decreased their insulin levels by 27% more than the control group.[40] The investigators noted that a strength of this study was its RCT design and the frequent PA measurements from the accelerometers.[40] Two limitations of this study are that the participants were men and the intervention group started with elevated levels of PA compared to the control group. These data suggest that insulin levels are inversely related to PA levels.

Additional biomarkers that could possibly be correlated with physical activity are blood lipids. The association of physical activity intensity and duration on HDL, LDL, and triglyceride (TG) levels was a studied by Da Silva et al..[41] This study was cross-sectional in design and included 12,688 participants with a mean age of 50.5 (±8.1) years. Data were extracted from the Brazilian Longitudinal Study of Adult Health (ELSA). Physical activity was measured using the IPAQ and lipid profiles were measured with 12 hour fasted blood draws. Physical activity was categorized as insufficient, moderate, or vigorous in this study.[41] When compared to insufficient physical activity, moderate physical activity showed a .89 mg/dl increase in HDL cholesterol, and vigorous physical activity was associated with a 1.71 mg/dl increase in HDL cholesterol.[41] Moderate physical activity was also associated with a .98 mg/dl decrease in TG levels while

vigorous suggested a reduction of .93 mg/dl when compared to insufficient physical activity.[41] Having more than 150 minutes per week of physical activity was associated with a decrease in TG of .98 mg/dl when compared to insufficient physical activity according to the authors.[41] No statistically significant results were found when examining LDL levels in the participants. Da Silva et al.[41] stated that the primary limitation of this study was due to the self-report nature of the IPAQ. Data from this study seem to suggest that physical activity intensity and duration can positively influence HDL and TG levels in adults.

Mestek writes that data on blood lipids and their relationship to physical activity seem to suggest that roughly a 1200kcal/week threshold of total energy expenditure of aerobic exercise is needed to produce alterations in HDL cholesterol for men and women.[42] The author also notes that these results should be generalizable because of the Heritage Family Study that found no differences in the effect of aerobic exercise on blood lipids based on race, age, and sex.[42] Mestek also reported that literature reviewed showed an inverse relationship between physical activity and total cholesterol.[42] Additionally, physical activity appears to have an inverse relationship to triglycerides, which is also reported as a prominent outcome for a number of studies.[42,43]

A confirmation of Mestek's report that physical activity lowers blood lipids was reported by Mbalilaki et al..[43] This study was completed in Tanzania and compared rural and urban population physical activity, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.[43] There were a total of 985 included participants in the study. The ages of women were 45.1 ± 9.3 in rural areas and 41.2 ± 8.2 in urban areas.

Men were ages 47 ± 9.2 in rural areas and 42 ± 7.8 in urban areas.[43] Cross-sectional data on physical activity, height, weight, and a non-fasting blood draw were collected at interviews. Physical activity levels were significantly higher in the individuals living in rural areas than those in urban areas.[43] Significantly lower weight, BMI, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides levels were observed in the rural group in comparison to individuals living in urban areas.[43] Limitations of this study were a cross-sectional design and physical activity levels were self-reported. The results of this study suggest that lower activity levels, due to urban living situations in this case, are significantly associated with abnormal lipid profiles.[43]

BMI is another biomarker that is widely used as a measurement basis for obesity and overweight statuses. Dyck et al.[44] suggest that physical activity may help prevent weight gain. These results were part of an analysis that included data from the International Physical Activity and the Environment Network Adult study (IPEN). This study included 5,712 adults (age 18 to 65 years, mean 43 ± 12.4).[44] In six countries, participants reported height and weight measures while another four countries had participants measured for height and weight. BMI was calculated from these data. Participants wore ActiGraph accelerometers for seven days in order to measure physical activity and sedentary time. The data showed a significant association between minutes of moderately vigorous physical activity and BMI.[44] The relationship between physical activity and BMI seemed to be curvilinear and the association was negative.[44] A weaker negative association was noted by the authors as the levels of moderately vigorous physical activity increased beyond 50 minutes per day.[44] Limitations of this study were

that the IPEN data were collected in a cross-sectional design and self-report was utilized for some height and weight measurements. The authors concluded that 60 minutes per day of moderately vigorous physical activity as recommended by the Institute of Medicine appear to be adequate for adults.[44]

A cardiometabolic risk factor that is studied alongside BMI is waist circumference. Waller et al.[45] investigated the effects physical activity on waist circumference and weight gain over a period of 30 years. The participants of this study came from the Finnish Twin Cohort, which is inclusive of every same sex twin born in Finland before 1958 and still alive during 1967.[45] Out of a possible 5,663 twin pairs, only 89 (age 18 – 48 mean 29, 40 male, 49 female) were included in the final results due to death and chronic disease. Baseline was measured at 1975 and 1981 using questionnaires to determine weight, height, smoking, alcohol use, and physical activity. A retrospective assessment was used to determine physical activity volume and vigorous physical activity participation in years 1980, 1985, 1990, 1995, 2000, and 2005.[45] A second assessment was given during these years to measure leisure time physical activity over the past year. Height, weight, and waist circumference were self-recorded in 2005 interviews and compared to the baseline data. The authors reported that waist circumference in 2005 was 4.1cm smaller in the active groups of twins than the inactive groups.[45] The authors studied weight gain as well and reported that although every pair of twins gained weight over the 30 year follow up, the active group gained an average of 2.8kg less weight than the inactive group.[45] These data suggest that physical activity is associated with lower amounts of weight gain and a reduced waist circumference in both men and women.

Limitations of this study are the small number of twin pairs and the absence of any dietary tracking. A strength is the long follow-up period. The investigators noted that although weight gain was present in both inactive and active groups, a smaller waist size in the active group is likely due to a reduction in abdominal fat.[45]

Sleep and Cardiometabolic Biomarkers:

In a cross-sectional study by Ford et al[17], the association of sleep duration and disorders with fasting and two hour glucose, insulin, and HbA1c was examined. There were a total of 11,815 adults who were ≥20 years (median 45).[17] Data were examined from the National Health and Nutrition Examination Survey from 2005 to 2010. Data for sleep apnea and sleep-disordered breathing were studied from 2005-2008. The authors reported that roughly 36% of participants reported less than six hours of sleep per night, 33% report snoring five or more times per week, and 4.2% reported having sleep apnea.[17] For participants that reported getting less than six hours of sleep per night, the mean concentration of insulin was 60.7 ± 1.5 pmol/L in men and 51.2 ± 1.4 pmol/L in women.[17] The group of participants sleeping less than six hours also had mean HbA1c levels of 5.43 ± .01.[17] The authors reported that the cross-sectional design of this study cannot suggest a direction of association.[17] Also, sleep duration was self-reported and could include inaccurate reporting from participants. The data from this study suggest that insulin and HbA1c concentrations may be significantly associated with durations of sleep less than 6 hours. The authors mentioned that this association may be mediated by BMI.[17]

In a study by Elder et al.[46], the relationship between sleep, activity, BMI, and waist circumference was examined. The number of participants included in this study was 337 from ages 18 to 65 y (mean 41.23 ± 13.99) and the data were utilized from the 2009-2010 NHANES.[46] Participants had a mean BMI of 29.11 (±6.79), waist circumference of 97.90 cm (±17.21), and sleep duration of 6.76 h (±1.38).[46] A significant inverse association between sleep duration and waist circumference was suggested after the Pearson r correlation coefficient analysis r(319) = -.113.[46] BMI did not have a significant association with sleep outcomes.[46] The authors reported that this study had a limitation due to the self-report nature of sleep duration data from participants.[46] A limitation that was not listed by the authors, but is commonly listed in other studies, is the cross-sectional study design of this investigation. Cross-sectional designs greatly limit the ability of researchers to suggest a causal relationship. The data from this study appear to suggest that waist circumference is inversely associated with sleep duration, but BMI was not associated with sleep outcomes.

C-reactive protein (CRP) is often found at elevated levels amongst those with sleep disturbances, such as obstructive sleep apnea syndrome (OSAS).[47] According to Bouloukaki et al., this relationship has caused much debate among those interested due to the numerous amount of confounding influences in many studies pertaining to the topic.[47] Bouloukaki et al. completed a smaller review of literature to summarize the relationship between OSAS and CRP.[47] The three main areas of concern to the authors were the roles of gender, obesity, and exercise. Gender is a very important confounding variable because numerous studies have suggested that women have higher CRP in comparison

with men.[47] Obesity is reported as a confounding factor in this relationship because some literature presents an independent relationship between OSAS and CRP, while others suggested that adjusting for obesity makes this relationship insignificant.[47] The authors noted that obesity is heavily present in individuals with OSAS, and the explanation for elevated CRP could be because BMI is significantly associated with CRP.[47] Along with these confounding factors, Bouloukaki et al. suggested that exercise may influence CRP levels.[47] This relationship is similar to CRP and obesity in that there seems to be no agreement in the literature endorsing its presence.[47] In non-obese patients with OSAS, the authors described no change of CRP after two months of physical activity.[47] It appears that literature currently focuses on sleep disturbances, such as OSAS, and their influences on CRP. The authors interpreted the results of their review as an inverse correlation between OSAS and CRP stating that patients with OSAS may have added health benefits, such as reductions in cardiovascular disease, if their treatment also reduces CRP.[47]

Blood lipids are an important biomarker that may be associated with sleep. However, the direction of this association is also not clear. In a study by Kinuhata et al.[48], sleep duration and the risk of abnormalities in lipid profiles in men was examined. This study included 7,627 Japanese men ages 40 to 55 y (mean 47.8 ± 4.2) from the Kansai Healthcare Study.[48] The Kansai Healthcare Study was ongoing at the time of this investigation, so participants that were enrolled between April 2000 and March 2001 were eligible. Mean baseline HDL cholesterol levels in participants who reported less than five hours of sleep were 54.7 mg/dl (±14.0), five to seven hours 56.7 mg/dl (±14.9), and seven or more hours 59.0 mg/dl (±16.4).[48] Mean baseline triglyceride levels in

participants who reported less than five hours of sleep were 116.0 mg/dl (range 82.0 – 170.0), five to seven hours 112.0 mg/dl (range 79.0 – 167.0), and seven or more hours 110.0 mg/dl (range 76.0 – 166.0).[48] At the six year follow-up point, incidence rates (per 1,000 person years) of low HDL cholesterol was 37.8 in the men who reported less than five hours of sleep, 27.7 in those who reported five to seven hours of sleep, and 19.4 in those who reported seven or more hours of sleep.[48] Six year follow-up incidence rates (per 1,000 person years) of high triglycerides were 59.6 in those who reported less than five hours of sleep, 44.1 in those who reported five to seven hours of sleep, and 47.3 in those who reported seven or more hours of sleep.[48] The authors reported that a limitation of this study was the fact that data were reported through self-report questionnaires.[48] Also, the question asking about sleep duration asked participants to report on sleep duration for the entire week, which may not allow for the separation of weekend and week nights according to Kinuhata et al..[48] One of the largest limitations this study has is that it was limited to middle age Japanese men, limiting the generalizability of the results to women, other ages, and even other countries.[48] The authors concluded that longer sleep duration was significantly associated with a decrease in the risk of future low HDL cholesterol and high triglycerides in middle age Japanese men.[48] The data from this study seem to suggest that sleep duration may independently influence blood lipid biomarkers.

The relationship between sleep and blood pressure is well studied. Literature suggests that blood pressure is influenced by sleep quality.[49,50] In a study by Wright et al., the relationship between sleep disordered breathing (SDB) and 24 hour ambulatory pressure was studied.[49] This was a five year study that included 42 (54%) female

participants with a mean age of 40 (±8.6) years.[49] Respiratory distress index (RDI) was assessed with an overnight monitoring examination baseline and follow-up.[49] Blood pressure was measured at baseline and follow-up with 13 30-minute interval measurements each. The authors reported that RDI was significantly associated with 24 hour mean systolic blood pressure, maximum diastolic blood pressure, mean sleep systolic blood pressure, and mean sleep diastolic blood pressure.[49] Strengths of this study were that the participants were normotensive, screened for medications, and that there was a large African American population included (26%).[49] A limitation noted by the authors was that because the population included in this study was normotensive at baseline, there may be an underestimation of the effect that SDB has on blood pressure.[49] The results of this study support the theory that blood pressure is influenced by sleep quality, but do not shed any light on the opposite direction of this relationship.

Physical activity Measurement:

Understanding how physical activity is measured and what current research speaks to in terms of recommended duration and intensity for health benefits is vital to establishing desired outcomes in this study. First, it is important to analyze the validity of subjective and objective measurements of physical activity in order to identify which type of measurement should be utilized and how accurate these measurements are.

A study by Ekblom et al.[51] was conducted to examine the predictive validity for metabolic syndrome of physical activity questions using accelerometers. The study included a total of 1111 participants (age 50 – 65 years) who agreed to wear ActiGraph

accelerometers for seven days. Participants needed to wear the accelerometers for a total of 600 minutes each day to be considered valid. For the subjective measurements, participants completed a questionnaire that inquired about lifestyle and living conditions. The authors reported that the median misclassification of time spent sedentary for participants was -185 minutes and -21.1 for moderately vigorous physical activity.[51] The authors declared that this study was limited by the variations in the number of participants that completed each question and due to the fact that some participants may have used the full hour option without considering the use of minutes in their self-reporting of physical activity.[51] The results from this study suggest that physical activity questionnaires may have low concurrent validity and may not be the most effective method to measure physical activity.

Physical activity intensity is often expressed as a metabolic equivalent of task (MET) or counts per minute (cpm) in accelerometers.[51,52] Ainsworth et al.[52] reported that a MET value for a resting activity would be one and then values increase in multiples of one beyond this point. The ratio of metabolic rate for an activity and resting metabolic rate is used to calculate intensities.[52] Certain accelerometers have the ability to measure triaxial data multiple times per minute.[51] Often, a range of numbers are used to determine intensities of movements. For example, Ekblom et al.[51] used a range of 0 to 199 cpm as sedentary time and 200 to 2689 cpm as light intensity physical activity for ActiGraph devices.

Recommendations of duration and intensity have been established using scientific research.[53] The recommendations for American adults per week are 150 minutes of

moderate intensity physical activity or 75 minutes of vigorous activity.[53] Blair and Powell[53] also state that current recommendations for physical activity suggest that adults participate in two days of strength training per week.

Sleep Measurement:

Objectively measured sleep is ideal when attempting to study the association of sleep and physical activity. In a study by Rosenberger et al.[54], the accuracy of nine different devices (ActiGraph GT3X+, activPAL, Fitbit One, GENEactiv, Jawbone Up, LUMOback, Nike Fuelband, Omron pedometer, Z-Machine) measuring a 24 hours period was compared. This study included 40 participants (mean age 36, range of 21-76) and required participants to wear the devices for 24 hours at a time.[54] Sleep data from the devices was compared to a Z-machine that measured brain activity.[54] Sedentary time had an error range of 9.5% to 65.8%, light physical activity had an error range of 19.7% to 28%, moderately vigorous physical activity had an error range of 51.8% to 92%, and steps had an error range of 14.1% to 29.9%.[54] Sleep measurement had an error range of 8.1% to 16.9%, but was still the lowest range of error out of all activities measured.[54] The authors report that a significant source of error may have been introduced by using measures that are not considered the gold standard in lab settings.[54] The results of this study suggest that objectively measured sleep from wearable devices may have significant error when compared to laboratory measurement, but shows the lowest amount of error if compared to other objectively measured activities with the same devices.

Sedentary Measurement

Sedentary behavior can be measured objectively with wearable sensors or by using self-report surveys. The difference between self-report and objective measurements is considerable for sedentary time. Harvey et al.[55] recorded sedentary times in older adults using a self-report survey and wearable sensors. 60% of older adults reported sitting for more than 4 hours per day, but when measured objectively, 67% of older adults sat for over 8.5 hours per day.[55] These data suggest that actual sitting time is difficult to obtain through self-report and wearable sensors should be used for accurate measurements.[55]

The activPAL is a wearable accelerometer that measures activity using posture and can even organize activity into categories of sitting/lying, standing, and stepping.[56] The activPAL has been found to be 100% accurate in a previous study when measuring sitting, standing, and stepping.[56] This accelerometer can estimate sitting and lying time by recording time spent in horizontal positions and standing by recording vertical positions.[56] Time spent lying and sitting are organized into epochs of various lengths (15 seconds in the Kozey-Keadle et al. study).[56] The activPAL can also measure step cadence and number of steps.[56] Kozey-Keadle et al. compared the precision of sedentary behavior measurements from the ActiGraph with those measured by the activPAL.[56] The activPAL had a bias of -7.7 minutes, while the ActiGraph had a bias of -16.9 minutes.[56] This shows that the activPAL is an effective tool when used to measure sedentary time in comparison to another validated wearable sensor.[56]

There appears to be a trend among past literature that suggests a correlation between physical activity and cardiometabolic biomarkers. It is also suggest in numerous studies that both physical activity and sleep are associated independently to cardiometabolic risk factors (e.g., glucose, insulin, blood lipids, BMI, and waist circumference).[28,38-42] After reviewing the literature on these relationships, there is a need for research concerning the mediation effects that sleep may have on a well-studied relationship between PA and cardiometabolic biomarkers.

CHAPTER 3

METHODS

Participants:

Eligible participants for the BeWell24 ASU and VA studies must have met the inclusion criteria as follows: age 35-65, BMI > 30, Trig > 150 mg/dl, HDL < 40/50, blood glucose >= 90 mg/dl, blood pressure > 130/85, a diagnosis of hypertension (Dx HTN), be sedentary, and have an android smartphone. The BeWell24 application was not compatible with iOS or other smartphone devices. Participants were excluded if they had seizure disorder, presence of serious illness, borderline personality disorder, bipolar disorder, any other unmanaged mental disorder, and unmanaged sleep apnea. Twenty nine participants were enrolled in the studies after meeting the inclusion criteria.

Recruitment:

Participants were recruited for the BeWell24 VA study by flyers and word of mouth at the Phoenix Veterans' Affairs Health Care System (PVAHCS). Recruitment for the BeWell24 ASU study was done through flyers and advertisements on ASU's MyASU webpage that affiliates of ASU are given access to. All participants completed a Qualtrics questionnaire to determine if they were eligible to participate in a first visit (considered week one) where full eligibility was confirmed and a fasting blood glucose measurement was assessed via finger prick. IRB approval was obtained for each BeWell24 study at both ASU and PVAHCS. Written consent was given by each participant at the start of this first visit before the finger prick took place.

Study Design:

The BeWell24 studies took place at Arizona State University and PVAHCS respectively. The BeWell24 studies were completed to study the effects of lifestyle interventions targeting sleep, sedentary behavior, and moderate-vigorous physical activity delivered via the BeWell24 phone app and to determine which combination of interventions was the most effective over an eight week period for lowering fasting blood glucose. Participants wore validated wrist and thigh accelerometers and were randomized into a combination of up to three lifestyle interventions delivered via the BeWell24 app.

BeWell24 Protocol:

Individuals were first directed to a Qualtrics survey to screen for type of phone, presence of sleep disturbances, physical activity levels, and sedentary time. Those who met the eligibility criteria (see section: *Participants*) were scheduled for a week one visit. During this visit, participants were tested for full eligibility after consent (see section: *Recruitment*). Study participants were also given a basic version of the BeWell24 application with no randomization to intervention groups. During the second visit on week 4 (baseline), participants partook in a fasted blood draw and had height, weight, and waist circumference measurements recorded. Each individual was randomized into an intervention group of either control (app with no intervention), sleep, physical activity, or sedentary time. Participants received an activPAL and GeneActiv during this visit and were instructed to wear these sensors for the next seven days. A return envelope was given so that the devices could be returned for quick data extraction before the devices

lost battery power. $25 in compensation was provided to study participants as well. These steps, with the exception of randomization, were completed for interim (week 8) and also posttest (week 12).

Measures

The BeWell24 studies included biomarker measurements for weight (kg), waist (cm), glucose (mg/dl), insulin (uU/ml), lipids (mg/dl), blood pressure (mm Hg), and C reactive protein (mg/L) during visits on week four (baseline), eight (interim), and twelve (post). Participants were asked to fast for nine hours prior to blood draws. Physical activity was measured using activPAL microsensors worn on participants' dominant thigh, and sleep from GENEActiv wrist accelerometers. Participants agreed to wear the accelerometers for one week intervals without removing them during baseline, interim and posttest weeks. Figure 1 depicts the potential mediators being proposed in the current study.

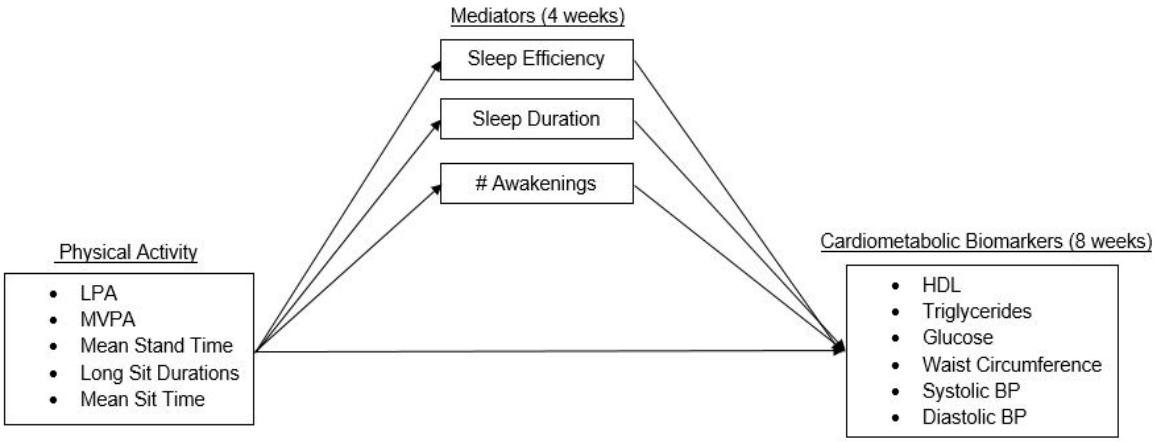

Figure 1. Proposed Mediators of Cardiometabolic Biomarkers

Physical activity and sedentary behavior. The primary outcomes of physical activity and sedentary behavior were assessed with the activPAL3 micro accelerometer (PAL Technologies, Glasgrow, United Kingdom) for seven days consecutively at each measurement time point. The activPAL provides a valid and reliable measure of posture (sitting vs. standing) for free-living settings[56,57] and uses a transducer that is appropriate for detecting lower intensity movements.[58] The activPAL was waterproofed using medical grade adhesive covering and attached to the midline of the thigh using a breathable, hypoallergenic tape. This method allowed for the monitor to be worn continuously for seven consecutive days without removing for bathing or other water-based activities (a valuable feature that reduces missing data). Additional adhesive dressing was given to all participants for re-application as necessary. The primary outputs of the activPAL are time spent sitting, time spent standing, and time spent "stepping." Time spent sitting is measured by the activPAL when it records a horizontal posture, which is why it is worn on the thigh. Standing time is a vertical non-moving posture measurement from the activPAL. Stepping can be measured by the activPAL when acceleration is detected from body movement. An additional output for moderate-vigorous physical activity was created when stepping was performed at a cadence ≥100 steps/minute. Only days with >10 hours of valid data were used, and valid days were summarized into weekly values.

Sleep. The GENEActiv accelerometer is a wrist-worn, waterproof, validated device that is designed assess physical activity and sleep in free-living settings.[59] This accelerometer

quantifies movement from participants every second for one week intervals. The data were summarized to 1-minute epochs for sleep analysis. Bed time and out of bed times were determined by self-report from the participants and verified by the investigators using GENEActiv data. The participants recorded times in the BeWell24 app that corresponded to their bed and wake times. Sleep periods were scored for sleep using the validated Sadeh[60] algorithm and data were summarized into total sleep duration (hours/night) and sleep quality metrics (i.e., awakenings per night, and sleep efficiency in %/night). Sleep efficiency is the percentage of time spent asleep while in bed. To calculate this, sleep time per night was subtracted from total in-bed times per night. Only nights with verified sleep were used and valid nights were summarized into weekly values.

Blood Analysis:

Fasted blood draws were taken at the beginning of visits two, three, and four. Approximately 15ml of blood was collected during each blood draw. The blood was drawn, stored, and analyzed by phlebotomists in the research lab of ASU in the ABC1 building.

Statistical Analysis:

The statistical program that was used for this study to analyze the BeWell24 data was SPSS (Version 23.x, IBM). Data are reported in mean ± (SE). Analysis of covariance (ANCOVA) was used to determine if physical activity produces any significant changes

in cardiometabolic risk factors (dependent variables) and sleep duration or quality measures (mediators). Covariate variables were interventions from the BeWell24 study (sleep, sedentary behavior, physical activity) and gender. Data for the change in sedentary behavior and physical activity from baseline to interim (weeks 4-8) were used as independent variables. The change in sleep duration and quality from baseline to interim (weeks 4-8) were used as mediator variables. Cardiometabolic biomarker changes from baseline to posttest (weeks 4-12) were used as dependent variables. This strategy was used to measure mediation prospectively and increase temporality. Strategies from Hayes' multiple mediator regression analysis were used to estimate mediation effects of all sleep measures that are significantly influenced by physical activity.[61] Gender and the possible influences of the BeWell24 intervention group assignments were controlled for in this investigation. Indirect effects in this study may not have been normally distributed due to the small sample size, which is why bootstrapping was used to re-sample the data 1,000 times. Bootstrapping has been promoted as an effective tool for estimating confidence intervals and making inferences.[62] Significant P values in this analysis are $<.05$.

CHAPTER 4

RESULTS

Table 1 presents baseline descriptive characteristics on age, race/ethnicity, cardiometabolic biomarkers, physical activity, and sleep duration and quality for participants included in this study. Participants were mostly Caucasian, male, possessing symptoms of metabolic syndrome, sedentary, and sleeping poorly.

Table 1. Baseline Characteristics

Characteristic	N (%)	Mean (SD)
Male	18 (62%)	
Age		52 (8.0)
Race/Ethnicity		
Caucasian	22 (76%)	
Hispanic	3 (10%)	
African American	3 (10%)	
Asian	1 (4%)	
Cardiometabolic Biomarkers		
HDL (mg/dl)		42 (16.9)
Triglycerides (md/dl)		148.6 (70.5)
Glucose (mg/dl)		115.6 (42.8)
Systolic BP		141.9 (17)
Diastolic BP		86 (12.8)
Waist Size (cm)		76.5 (31.9)
Physical Activity		
Sitting Time (min/day)		489.8 (148.9)
Standing Time (min/day)		270.3 (143.2)
LPA (min/day)		62.4 (34.1)
MVPA (min/day)		14.3 (7.4)
Long Sitting Durations (min/day		288.3 (108.4)
Sleep Duration and Quality		
Sleep Efficiency (%)		71.6 (11.9)
Sleep Duration (hour/day)		4.2 (1.9)
Awakenings (number/night)		8.5 (3.9)

Abbreviations: LPA, light physical activity; MVPA, moderately vigorous physical activity; Sleep Efficiency, time in bed - time asleep; Long Sit Duration, sitting time

Table 2 presents the mediation results of sleep duration and quality on the effect of long bouts of sitting (>30min) on cardiometabolic biomarkers. Long bouts of sitting significantly affected triglycerides, however the total and specific variable indirect effects did not mediate this effect. Long bouts of sitting did not have a significant direct effect on HDL levels, glucose levels, waist circumference, or blood pressure.

Table 2. Mediation of the Effect of Long Bouts of Sitting on Eight Week Cardiometabolic Biomarker Outcomes through Sleep Efficiency, Sleep Duration, and Number of Awakenings.

	Point		Bootstrapped 95% CI	
Variable	Estimate	*SE*	Lower	Upper
HDL	-0.01	0.01	-0.02	0.01
TOTAL	0.00	0.01	0.00	0.02
Sleep Efficiency	0.00	0.00	-0.01	0.00
Sleep Duration	0.00	0.01	0.00	0.03
Awakenings	0.00	0.01	-0.02	0.01
Triglycerides	**0.15**	**0.07**	**<.01**	**0.29**
TOTAL	0.01	0.04	-0.06	0.11
Sleep Efficiency	0.00	0.02	-0.05	0.03
Sleep Duration	0.01	0.05	-0.06	0.14
Awakenings	0.00	0.04	-0.10	0.07
Glucose	0.08	0.05	-0.03	0.18
TOTAL	0.00	0.03	-0.04	0.11
Sleep Efficiency	0.00	0.02	-0.03	0.06
Sleep Duration	0.00	0.03	-0.03	0.12
Awakenings	0.00	0.03	-0.06	0.07
Waist Circumference	0.02	0.03	-0.05	0.08
TOTAL	-0.01	0.03	-0.09	0.03
Sleep Efficiency	0.00	0.02	-0.02	0.05
Sleep Duration	-0.01	0.03	-0.13	0.02
Awakenings	0.00	0.02	-0.02	0.06
Systolic BP	0.01	0.02	-0.03	0.06
TOTAL	0.00	0.01	-0.05	0.02
Sleep Efficiency	0.00	0.01	-0.01	0.03
Sleep Duration	-0.01	0.02	-0.08	0.01
Awakenings	0.00	0.02	-0.02	0.03
Diastolic BP	0.00	0.01	-0.03	0.03
TOTAL	0.00	0.01	-0.02	0.02
Sleep Efficiency	0.00	0.00	-0.01	0.01
Sleep Duration	0.00	0.01	0.00	0.04
Awakenings	0.00	0.01	-0.01	0.01

Notes . **Bold** denotes CI does not contain zero and is significant.
1,000 bootsrap samples.

Table 3 presents the mediation results of sleep duration and quality on the effect of light physical activity on cardiometabolic biomarkers. Light physical activity did not have a significant direct effect on HDL levels, triglycerides, glucose levels, waist circumference, or blood pressure.

Table 3. Mediation of the Effect of Light Physical Activity on Eight Week Cardiometabolic Biomarker Outcomes through Sleep Efficiency, Sleep Duration, and Number of Awakenings.

	Point		Bootstrapped 95% CI	
Variable	Estimate	*SE*	Lower	Upper
HDL	0.03	0.05	-0.08	0.13
TOTAL	-0.01	0.05	-0.15	0.06
Sleep Efficiency	0.00	0.02	-0.06	0.03
Sleep Duration	0.02	0.07	-0.02	0.32
Awakenings	-0.03	0.05	-0.34	0.01
Triglycerides	-0.13	0.41	-0.97	0.72
TOTAL	0.00	0.25	-0.41	0.64
Sleep Efficiency	-0.01	0.11	-0.28	0.20
Sleep Duration	0.09	0.31	-0.16	1.53
Awakenings	-0.08	0.29	-1.28	0.24
Glucose	-0.27	0.27	-0.83	0.30
TOTAL	0.03	0.23	-0.40	0.55
Sleep Efficiency	0.01	0.10	-0.15	0.31
Sleep Duration	0.04	0.32	-0.19	1.04
Awakenings	-0.02	0.21	-0.57	0.26
Waist Circumference	-0.26	0.16	-0.60	0.07
TOTAL	-0.01	0.13	-0.29	0.23
Sleep Efficiency	0.01	0.12	-0.13	0.35
Sleep Duration	-0.11	0.23	-0.94	0.16
Awakenings	0.09	0.15	-0.02	0.87
Systolic BP	-0.12	0.11	-0.34	0.10
TOTAL	0.02	0.10	-0.16	0.23
Sleep Efficiency	0.01	0.06	-0.08	0.15
Sleep Duration	-0.06	0.18	-0.73	0.07
Awakenings	0.07	0.12	-0.03	0.48
Diastolic BP	-0.05	0.07	-0.19	0.09
TOTAL	0.03	0.05	-0.05	0.15
Sleep Efficiency	0.00	0.03	-0.05	0.06
Sleep Duration	0.02	0.05	-0.02	0.25
Awakenings	0.00	0.05	-0.09	0.09

Notes. 1,000 bootsrap samples.

Table 4 presents the mediation results of sleep duration and quality on the effect of moderately vigorous physical activity on cardiometabolic biomarkers. Moderately vigorous physical activity did not have a significant effect on HDL levels, triglycerides, glucose levels, waist circumference, or blood pressure.

Table 4. Mediation of the Effect of Moderately Vigorous Physical Activity on Eight Week Cardiometabolic Biomarker Outcomes through Sleep Efficiency, Sleep Duration, and Number of Awakenings.

			Bootstrapped 95% CI	
Variable	Point Estimate	*SE*	Lower	Upper
HDL	0.17	0.18	-0.20	0.54
TOTAL	-0.07	0.18	-0.50	0.25
Sleep Efficiency	0.00	0.08	-0.07	0.26
Sleep Duration	-0.07	0.21	-0.54	0.28
Awakenings	-0.01	0.15	-0.39	0.18
Triglycerides	-1.63	1.42	-4.59	1.34
TOTAL	-0.15	0.99	-1.58	2.32
Sleep Efficiency	0.02	0.59	-0.76	1.29
Sleep Duration	-0.16	0.94	-2.43	1.34
Awakenings	-0.01	0.59	-1.47	0.98
Glucose	-0.29	1.00	-2.37	1.80
TOTAL	-0.16	0.92	-2.42	1.61
Sleep Efficiency	-0.04	0.48	-1.14	0.67
Sleep Duration	-0.11	0.90	-2.77	1.14
Awakenings	-0.01	0.53	-1.22	0.81
Waist Circumference	-0.73	0.60	-1.97	0.52
TOTAL	0.34	0.59	-0.63	1.72
Sleep Efficiency	-0.06	0.45	-0.95	0.66
Sleep Duration	0.38	0.74	-0.69	2.11
Awakenings	0.02	0.33	-0.31	1.11
Systolic BP	-0.27	0.39	-1.07	0.54
TOTAL	0.17	0.42	-0.63	1.04
Sleep Efficiency	-0.04	0.24	-0.54	0.33
Sleep Duration	0.19	0.56	-0.87	1.07
Awakenings	0.01	0.31	-0.33	1.33
Diastolic BP	0.02	0.24	-0.48	0.52
TOTAL	-0.08	0.21	-0.50	0.29
Sleep Efficiency	0.00	0.11	-0.39	0.14
Sleep Duration	-0.07	0.18	-0.60	0.18
Awakenings	0.00	0.13	-0.25	0.20

Notes. 1,000 bootsrap samples.

Table 5 presents the mediation results of sleep duration and quality on the effect of daily standing time on cardiometabolic biomarkers. Daily standing time did not have a significant effect on HDL levels, triglycerides, glucose levels, waist circumference, or blood pressure.

Table 5. Mediation of the Effect of Daily Standing Time on Eight Week Cardiometabolic Biomarker Outcomes through Sleep Efficiency, Sleep Duration, and Number of Awakenings.

			Bootstrapped 95% CI	
Variable	Point Estimate	*SE*	Lower	Upper
HDL	0.00	0.01	-0.01	0.02
TOTAL	0.00	0.01	-0.02	0.02
Sleep Efficiency	0.00	0.01	-0.01	0.02
Sleep Duration	-0.01	0.01	-0.04	0.01
Awakenings	0.00	0.01	0.00	0.04
Triglycerides	-0.02	0.07	-0.16	0.13
TOTAL	0.00	0.08	-0.29	0.08
Sleep Efficiency	0.01	0.04	-0.04	0.12
Sleep Duration	-0.03	0.11	-0.34	0.09
Awakenings	0.02	0.07	-0.08	0.22
Glucose	-0.04	0.05	-0.14	0.05
TOTAL	-0.01	0.04	-0.16	0.04
Sleep Efficiency	-0.01	0.04	-0.11	0.05
Sleep Duration	-0.01	0.06	-0.17	0.10
Awakenings	0.01	0.05	-0.06	0.14
Waist Circumference	-0.01	0.03	-0.07	0.05
TOTAL	0.01	0.04	-0.06	0.10
Sleep Efficiency	-0.01	0.03	-0.11	0.01
Sleep Duration	0.04	0.05	-0.02	0.21
Awakenings	-0.01	0.03	-0.15	0.03
Systolic BP	-0.02	0.02	-0.06	0.02
TOTAL	0.00	0.02	-0.03	0.06
Sleep Efficiency	-0.01	0.02	-0.04	0.01
Sleep Duration	0.02	0.03	-0.01	0.12
Awakenings	-0.01	0.02	-0.08	0.01
Diastolic BP	0.00	0.01	-0.03	0.02
TOTAL	-0.01	0.01	-0.04	0.00
Sleep Efficiency	0.00	0.01	-0.02	0.01
Sleep Duration	-0.01	0.02	-0.05	0.01
Awakenings	0.00	0.01	-0.01	0.03

Notes. 1,000 bootsrap samples.

Table 6 presents the mediation results of sleep duration and quality on the effect of daily sitting time on cardiometabolic biomarkers. Daily sitting time did not have a significant effect on HDL levels, triglycerides, glucose levels, waist circumference, or blood pressure.

Table 6. Mediation of the Effect of Daily Sitting on Eight Week Cardiometabolic Biomarker Outcomes through Sleep Efficiency, Sleep Duration, and Number of Awakenings.

	Point		Bootstrapped 95% CI	
Variable	Estimate	*SE*	Lower	Upper
HDL	0.00	0.01	-0.02	0.01
TOTAL	0.00	0.01	0.00	0.02
Sleep Efficiency	0.00	0.00	-0.01	0.00
Sleep Duration	0.01	0.01	0.00	0.03
Awakenings	0.00	0.00	-0.02	0.00
Triglycerides	0.09	0.06	-0.04	0.21
TOTAL	0.00	0.05	-0.07	0.14
Sleep Efficiency	-0.01	0.03	-0.08	0.02
Sleep Duration	0.02	0.07	-0.08	0.22
Awakenings	-0.01	0.04	-0.15	0.04
Glucose	0.03	0.04	-0.06	0.11
TOTAL	0.01	0.03	-0.02	0.11
Sleep Efficiency	0.00	0.02	-0.02	0.10
Sleep Duration	0.01	0.04	-0.06	0.13
Awakenings	-0.01	0.02	-0.09	0.03
Waist Circumference	-0.02	0.03	-0.07	0.04
TOTAL	-0.01	0.02	-0.05	0.04
Sleep Efficiency	0.01	0.02	-0.01	0.07
Sleep Duration	-0.03	0.03	-0.12	0.01
Awakenings	0.01	0.02	-0.01	0.09
Systolic BP	0.01	0.02	-0.02	0.05
TOTAL	0.00	0.01	-0.04	0.02
Sleep Efficiency	0.01	0.01	-0.01	0.04
Sleep Duration	-0.02	0.02	-0.10	0.01
Awakenings	0.01	0.01	0.00	0.06
Diastolic BP	0.00	0.01	-0.02	0.02
TOTAL	0.01	0.01	0.00	0.03
Sleep Efficiency	0.00	0.01	-0.01	0.02
Sleep Duration	0.01	0.01	0.00	0.04
Awakenings	0.00	0.01	-0.02	0.01

Notes. 1,000 bootsrap samples.

CHAPTER 5

DISCUSSION

This study examined the relationship between physical activity and cardiometabolic biomarkers while also assessing the mediation effect of sleep on this relationship. The results of this investigation demonstrate that long bouts of sitting influence triglyceride levels and there is no mediation of this effect by sleep quality or duration. The effect was relatively small. These findings are consistent with other research in this area showing reductions in triglyceride levels after interruptions in sitting time throughout the day.[63] Other measures of sedentary time and physical activity were not found to have a significant direct effects on cardiometabolic biomarkers and therefore mediation is not possible in these relationships. Possible reasoning for this could be because the BeWell24 studies were conducted over eight weeks with primary outcomes of physical activity, sedentary time, and sleep quality and duration. Eight weeks may too short of a timeframe to see significant changes in biomarker measurements. Increasing the study duration may provide larger direct and indirect effects on cardiometabolic biomarker measurements and allow for more reliable tests of mediation. Controlling for the behavior changes influenced by the BeWell24 interventions may have biased the results to the null as well.

Prolonged Sitting:

Long durations of sitting can have numerous negative effects on metabolic health, even in adults who actually meet the minimum recommendations for moderate-vigorous

physical activity.[64] It is important to note that physical activity and sedentary behaviors need to be addressed separately and not together, although physical activities may be used to interrupt and decrease sitting time. A previous study reported that individuals who reported high levels of moderately vigorous physical activity and partook in television viewing for longer than seven hours per day had a 50% greater risk of death from all causes.[64] In light of this grim outlook on prolonged sitting time, there has been a plethora of research on strategies to reduce sitting time. Studies have suggested that providing passive prompts on computers at work, encouraging standing meetings, and in-person communication may be feasible and effective methods to interrupt bouts of sitting throughout the day.[65,66] Opportunities for future studies on prolonged sitting should focus on establishing a dose-response relationship and how to encourage maintenance of these interventions.[67] Given the global scale of excess sedentary behaviors, it is also important to understand the external influences on sedentary behaviors in order to create population level initiatives with high efficacy. Administering sedentary behavior interventions on a population level will require a robust understanding of sedentary behavior mechanisms and the associated health outcomes. There is a great deal of evidence in this field, but more experimental data must be gathered quickly to curb increasing detrimental health outcomes.

Health Impact of Triglycerides:

Previous literature has suggested that triglycerides are positively associated with BMI, plasma glucose, systolic blood pressure, and diastolic blood pressure, all of which

are components of metabolic syndrome.[68] This association rises over time, indicating an increased risk for metabolic syndrome due to prolonged exposure to elevated triglyceride levels.[68] These data suggest that reducing long bouts of sitting may be an effective complementary treatment to current pharmaceutical methods for metabolic syndrome. The prevalence of metabolic syndrome in the U.S. alone is 35% for adults and 50% in older adults over the age of 60.[69] With uncertainty in the health insurance industry and the rising age of adults, especially in the U.S., cost effective methods of treatment for metabolic syndrome have never been more valuable.

Strengths:

The primary strength of this study was the objective measurement of sleep and physical activity using validated wrist and thigh sensors. Many studies use self-report methods of measurement for sleep or physical activity measurements, which can limit the reliability of outcomes. This study was also prospective in nature, testing mediation over a period of eight weeks. By using independent and mediator variables at baseline and four weeks (interim) and mediation effects on dependent variables at eight weeks (posttest), temporality is strengthened in the results. Another strength was the goals of the BeWell24 intervention that targeted physical activity, sleep, and sedentary behaviors. These made it an optimal context to test mediation effects.

Limitations:

Limitations of this study may include a response bias due to the wearing of accelerometers for sleep and physical activity purposes. In addition, the small sample size of BeWell24 may have limited the statistical power to identify direct and indirect effects. This population may be a limitation as well. Participants began the BeWell24 study sleeping very poorly in both duration and quality measurements. Changing these outcomes can be difficult if participants are suffering from sleep apnea, PTSD, or other common disabilities found in veteran populations specifically. Lastly, the effect size of physical activity on triglycerides was very small. This small effect size may not have been enough to detect any mediation effects that could be present with a larger direct effect.

Future Studies:

Limitations may have greatly impacted the results of this study. There are recommendations for future studies similar in nature that should be considered. The length of a future study should be increased to potentially see more variation in cardiometabolic variables. Eight weeks should be enough time to see change in cardiometabolic variables if an effect is present from independent or mediator variables, but the behavior changes influenced by the BeWell24 interventions were controlled for. Also, this study reported a very small effect among all variables, even in the one significant relationship between long bouts of sitting and triglycerides. The goal of research in the future should be to increase the physical activity, sedentary behavior, and

sleep effects in participants without controlling for these influences in order to have a true measurement of mediation. To accomplish this, participants can be instructed on specific physical activities to complete each week or an environment with physical activities can be provided, such as a park. Reductions in sedentary time can be influenced by personal reminders to stand or walk around. Even items such as standing desks may be able to reduce sitting times if funding is present. Sleep may be difficult to influence as there are many disturbances specific to individuals. Sending reminders to participants at bed times or before periods that should be used to prepare for bed may assist with increasing sleep duration and quality.

CHAPTER 6

CONCLUSION

Middle age adults who reduce prolonged sitting periods are more likely to see reductions in triglyceride levels. Further study on triglycerides acting as a mediator to the relationship between physical activity and other cardiometabolic risk factors should be conducted in light of the results of this study and previous literature.

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