# Examining Sleep Patterns and Cardiovascular Disease Risk Profiles in Community-Dwelling Middle Age and Older Females

By

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## Abstract

Poor sleep patterning is associated with increased risk for future adverse cardiovascular events. An exaggerated blood pressure response (EBPR) to a moderate bout of physical activity may better and earlier detect autonomic dysfunction and CVD risk compared with resting blood pressure (BP). To date, determining if poor sleep patterning is associated with an EBPR to 3-minutes of moderate physical activity has not yet been assessed. The purpose of my thesis is to determine if differing sleep patterns are associated with an EBPR to 3-minutes of moderate physical activity in 206 women aged 55 years or older. Objective sleep data was collected through accelerometry to assess both sleep duration (total sleep time; TST; sleep duration$_{TST}$) and sleep quality (sleep efficiency; SE; Sleep Quality$_{SE}$). Self-reported sleep quality data was also collected using the Pittsburgh Sleep Quality Index (PSQI; sleep quality$_{PSQI}$). The BP response was collected after 3-minutes of moderate physical activity performed on a treadmill and categorized into a typical BP response or an absolute or relative EBPR (EBPR$_{Absolute}$; EBPR$_{relative}$). Differing sleep patterning prevalence was classified as: 1) 40.8% of the cohort had short sleep duration$_{TST}$, 57.3% had normal sleep duration$_{TST}$ and 1.9% had long sleep duration$_{TST}$; 2) 4.9% had poor sleep quality$_{SE}$, and 95.1% had adequate sleep quality$_{SE}$; and, 3) 57.3% had poor sleep quality$_{PSQI}$ and 42.7 had adequate sleep quality$_{PSQI}$. No significant associations were determined between the objectively measured sleep duration$_{TST}$ or sleep quality$_{SE}$ and EBPR categories. A significant association between sleep quality$_{PSQI}$ and an EBPR$_{relative}$ was detected, where participants with better sleep quality$_{PSQI}$ score had a 63% reduction of having an EBPR$_{relative}$. The findings of no association between sleep duration$_{TST}$ or sleep quality$_{SE}$ variables may be due to my study's limitation of a small sample size and the large amount of variance. These associations should be re-assessed while using a larger sample size. If

this relationship is confirmed in the future, health care professionals could implement sleep interventions to reduce CVD risk.

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## Dedication

This thesis is dedicated to my family who have provided me endless love and support through all my academic and life pursuits.

## List of Abbreviations

BP- Blood pressure

EBPR- Exaggerated blood pressure response

PSQI- Pittsburgh sleep quality index

SE- sleep efficiency

TST- total sleep time

PSG- Polysomnography

REM- rapid eye movement

NREM- non rapid eye movement

EEG- electroencephalogram

EMG- electromyography

EOG- electrooculography

SWS- short wave sleep

ANS- autonomic nervous system

HCV- hepatitis C-virus

CSF- cerebral spinal fluid

CVD- cardiovascular disease

CHD- coronary heart disease

ESG- European Society of Cardiology

NHS- Nurse's Health Study

AHA- American Heart Association

METs- Metabolic equivalents

WARM- Women's Advanced Risk Assessment in Manitoba

SROBE- Strengthening the Reporting of Observational Studies in Epidemiology

mmHg- millimetre of mercury

Sleep duration$_{TST}$- Sleep duration assessed by TST

Sleep Duration$_{continuous}$- Sleep duration assessed by TST as a continuous variable

EBPR$_{Absolute}$- Exaggerated Absolute Blood Pressure Response

Typical$_{Absolute}$ Response- Typical Absolute Blood Pressure Response

EBPR$_{Relative}$- Exaggerated Relative Blood Pressure Response

Typical$_{Relative}$ Response- Typical Relative Blood Pressure Response

Sleep Quality$_{SE}$- Sleep Quality assessed scored by Sleep Efficiency assessed by accelerometry

SE$_{Continuous}$- Sleep Efficiency assessed by accelerometry as a continuous variable

Sleep Quality$_{PSQI}$- Sleep Quality assessed by PSQI

## Table of Contents

## List of Tables

## List of Figures

# Chapter 1: Literature Review

This literature review will cover the basic physiological changes associated with poor sleep patterning including both sleep duration and sleep quality. Accessible methods of identifying poor sleep patterning will be discussed in comparison to the gold standard measurement of sleep. The review will then shift to examine exaggerated blood pressure (BP) response to moderate intensity exercise as a measurement of cardiovascular disease risk. The definition of exaggerated BP in response (EBPR) to moderate intensity exercise, how it is assessed and the association with sleep patterning will then be examined. Finally, the review will identify knowledge gaps between sleep patterning and an exaggerated BP response to moderate-physical activity.

## 1.1 Sleep

Humans sleep for approximately one-third of their lives[1]. Stats-Canada data from 2007-to-2013 report that Canadians aged 18 to 64 averaged 7.12 hours of sleep per night. Although some individuals think of sleep as one state, it is more accurate to recognize that sleep is divided into two distinct states: rapid eye movement (REM) sleep[1], also called active sleep or paradoxical sleep and non-rapid eye movement (NREM) sleep[2]. REM sleep consists of a single stage; whereas historically NREM sleep consists of 4 stages (S1-S4)[1][2,3]. Contemporary research now recognizes NREM stages 3-4 as one stage referred to as N3[3]. REM sleep accounts for approximately 20-25% of sleep, where NREM sleep accounts of approximately 75% - 80%[4]. Each phase and stage represent the relative depth of sleep and have unique characteristics as demonstrated by brain waves, muscle tone, and eye movement patterns. S1 is the shallow stage of sleep where a person is still easily awoken and lasts approximately 1 to 7 minutes[4]. Electroencephalogram (EEG) of this S1 phase is characterized by rhythmic alpha waves at a frequency of 8 to 13 cycles per second[1]. After the S1 phase is complete, a person enters S2,

which lasts approximately 10-25 minutes in the initial cycle of sleep[4]. S2 then progresses to be 50% of the total sleep cycle later in the night[4]. S2 is a much deeper sleep than S1, but individuals can still be awoken by stimulation. Brainwave activity on an EEG is low voltage and is characterized by the frequent occurrence of sleep spindles and K-complexes[5]. Current theories suggest that memory consolidation occurs primarily during this stage. N3 in NREM accounts for approximately 20% of total sleep time and is defined as deep sleep or slow wave sleep (SWS)[2,5]. Deep sleep is defined by changes in EEG patterns compared to REM. Deep sleep is regarded as the refreshing, restorative part of sleep, however, it is not clear what substrate in the body or brain is restored. N3 lasts about 20-40 minutes, where EEG is characterized by high voltage, slow wave frequency[3]. After an individual progresses through NREM, REM sleep occurs which is the phase of sleep responsible for dreaming which an individual can remember after waking. It is characterized by total body voluntary muscle paralysis (except for respiratory and extraocular muscles)[3].

In normal conditions, sleep progresses in the order from S1 to S4 followed by REM sleep approximately 4-6 times per night[1]. The organization of the sleep stages and the distribution of those stages is known as “sleep architecture”[1]. NREM and REM sleep stages alternate lasting 60-120min[1]. After the completion of REM sleep, the cycle restarts with a brief period of wakefulness before the cycle begins again. This cycle of NREM, REM and wakefulness is repetitive in nature, where cortical activity of the brain undergoes regular cyclic changes between NREM and REM sleep. The sleep cycles repeat 4-6 times throughout a typical night-time sleep period lasting >7.0-<9.0 hours[4].

During the day, BP values can increase through mechanisms such as postural changes, exercise, and caffeine consumption. During NREM sleep, physiological variables such as heart

rate, respiration and cortical activity decrease, body temperature decreases, and energy consumption is lower[2]. NREM sleep is characterized by progressive BP and HR decreases which becomes more pronounced from stage 1-3[6]. The reduction in BP is due to the decrease in heart rate and in sympathetic vasoconstrictor tone[6]. However, during REM sleep BP is increased compared to wakefulness[6]. The normal reduction in BP, compared to mean daytime values, during sleep is 10% to 20% in healthy, normotensive individuals[6,7]. This phenomenon is referred to as “dipping”, while non-dippers are defined as a BP reduction <10%. Nocturnal BP dipping is important for BP regulation during the day[8]. It is known that the autonomic nervous system (ANS) is influenced by sleep, while the ANS regulates cardiovascular function through the sympathetic and parasympathetic nervous system[6]. The association between cardiovascular health and sleep patterning may result from a still unknown, common pathogenic mechanism.

Two main components of physiological sleep regulation include homeostatic and circadian components[1]. The homeostatic component of sleep tracks the duration of the previous wakefulness period, where the longer we stay awake, the longer and deeper the following sleep will be. The amount of REM in each cycle progresses throughout the night from being minimal on initiation of sleep, but eventually is up to 30% of the cycle later in the night[2]. The second, circadian component regulates the timing of sleep typically over a 24 hr period[2]. Homeostatic and circadian components create the two factors of the two-process model describing the regulation of sleep[5] (Figure 1). Shown graphically below, homeostatic sleep drive typically increases throughout the day, increasing the need to sleep, but it is countered and moderated by the circadian drive. Homeostatic sleep is greatest in the late evening, and slowly decreases throughout the sleep period. During this sleep period, the circadian drive begins to overcome the homeostatic sleep drive, which triggers awakening.

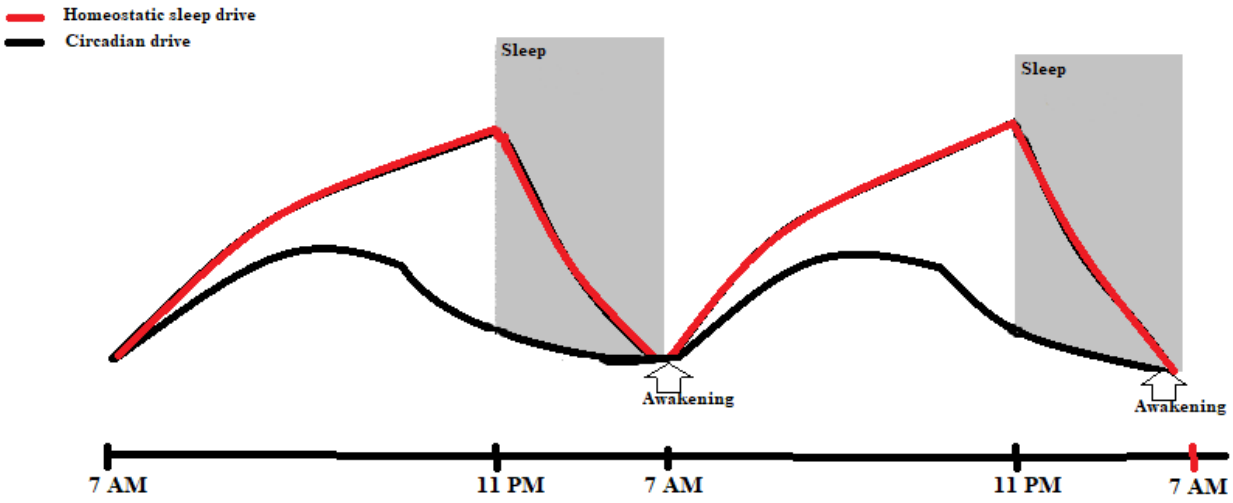



*Figure 1: "Adapted" Two-process model of sleep from Borbely et. al (2016)*[9]

## 1.2 The Physiological Need of Sleep

Despite the advances in sleep research, the greatest mysteries that remain to be determined are, why is sleep a restorative state and why does a lack of sleep impair physiological function. It is possible that sleep serves many purposes. Lack of sleep reduces learning, impairs performance on cognitive tests, and prolongs reaction time[10]. Many theories through research have been developed to understand why we sleep. Some of these theories include 1) memory theory 2) immunity theory and the 3) beta-amyloid theory. These theories will be briefly explained in the literature review to demonstrate the importance of sleep through a multidimensional approach.

**Memory Theory**

There has been as increasing number of studies that have shown an association between sleep and memory. The first evidence of the relationship between sleep and memory was in 1924 which focused on declarative memory[11]. More recently research has focused on memory consolidation and sleep. With memory consolidation, it is likely that there are different

neurological processes at work during the various sleep stages. It has been demonstrated that sleep enhances memory consolidation by providing an optimal endocrine environment, by temporarily augmenting cortisol, preventing hormonal feedback signals from interfering with memory processing[11]. The physiological mechanisms behind sleep and memory are far from being well-established and further research is needed to understand the relationship between them.

**Immunity Theory**

Throughout research the relationship between sleep and the immune system has been intensively studied. Starting in the 1980s, the sleep response to infectious challenges have been studied in animal models[5]. The immune system is the body's defense system which can determine any internal or external threats that may cause harm to the physiological system. Findings in both animal and human models have shown pathogens or their components are able to alter sleep patterning[12]. For example, sleep disturbances are commonly demonstrated in chronic infection with hepatitis C virus (HCV). More than 50% of patients diagnosed with HCV reported feeling fatigue, excessive daytime sleepiness and poor sleep quality[13]. As well, an objective sleep assessment using actigraphy demonstrated an increased nighttime wake time and reduced sleep efficiency (SE) in women diagnosed with HCV[12]. Sleep disturbances are also commonly found in diseases with inflammatory pathophysiology, such as inflammatory bowel diseases[5].

**Beta-Amyloid Theory**

The last theory focuses on beta-amyloid, a protein linked to neurodegenerative diseases which is commonly found in the interstitial space surrounding the cells of the brain. When this

protein builds up in large amounts around the brain, normal brain functioning can be impaired. In the peripheral tissues, the lymph vessel returns the excess proteins to the general circulation for degradation in the liver. The brain lacks this conventional lymphatic transport system for toxic waste. In the brain, the cerebral spinal fluid acts as this transport system, known as the glymphatic system[14] where it recirculates interstitial fluid in and around the brain while removing the toxic beta-amyloid proteins. The interstitial concentration of beta-amyloid is higher during wakefulness due to the increase in production. Xie et al. demonstrated in rodents that the restorative function of sleep may be due to the switching of the brain into a functional state that facilitates the clearance of degradation products of neural activity that accumulate during wakefulness such as beta amyloid[10]. Xie et al.'s analysis demonstrated that the cortical interstitial space increases by more than 60% during sleep, resulting in efficient convective clearance of Aβ and other compounds[10].

### 1.3 Sleep Patterns

Sleep patterning is a term used to describe both sleep duration and sleep quality. Sleep duration is defined as either short, normal or long sleep. Short sleep has most often been defined as $\leq$7[15] hours/night; whereas, long sleep has been defined as $\geq$ 9 hours/night[15]. The National Sleep Foundation recommend that adults obtain $\geq$7 and <9 hours of sleep per night[16] (Table 1), which in this thesis will be defined as normal sleep[17]. Research from the Cancer Prevention Study 1 (CPSI) of over 1.1 million participant demonstrated a U-shaped relationship between sleep and health (Figure 2), where the most extreme ends of sleep are associated with adverse health outcome[18]. Both short, defined as $\leq$6 hours per night (Table 1), and long, defined as $\geq$9 hours per night (Table 1) sleep length has been demonstrated as a potential lifestyle factor that impacts CVD[19].

*Table 1: Sleep Definitions*

| **Sleep Terms** | **Study Definitions** |
|---|---|
| Sleep architecture | Organization of sleep into several stages and the distribution of those stages across time[1] |
| Sleep quality | Objectively measured as the percentage of sleep efficiency (SE), where SE is equal to percent total sleep time/time in bed (TST/TIB x 100%);<br><br>Subjective evaluation of sleep can be measured through the Pittsburgh Sleep Quality Index (PSQI), recorded as a total score out of 21 points[20] |
| Sleep Patterning | A general term used to combine sleep duration and sleep quality[2] |
| Sleep Deprivation | The situation or condition of suffering from a lack of sleep[4] |
| Sleep Duration | The total sleep time (TST), in hours, an individual sleeps per night[21]. |
| Normal sleep duration | ≥7-<9 hours of sleep per night[15] |
| Long sleep duration | ≥9 hours of sleep per night[22] |

| | |
|---|---|
| Short sleep duration | <7 hours of sleep per night[23] |
| Poor sleep quality | Sleep efficiency < 85% based on ActiLife Analysis[24] Or PSQI score ≥5[20] |
| Adequate sleep quality | Sleep efficiency ≥85% based on ActiLife Analysis[24] Or PSQI score <5[20] |

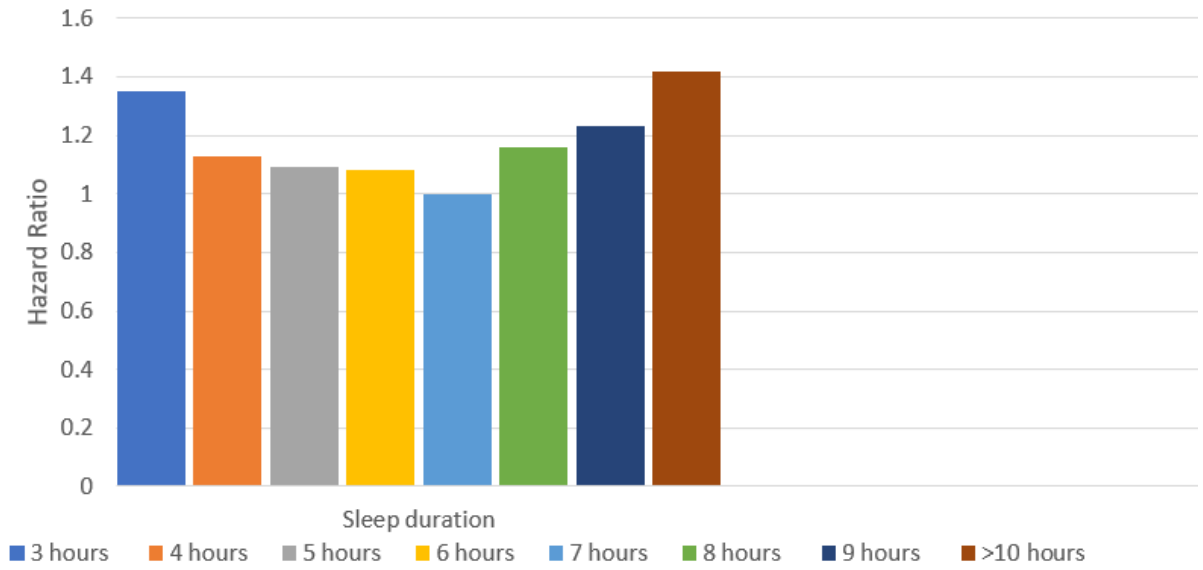


**Figure 2:** "Adapted" Kripke 2002, U-shaped relationship demonstrated through hazard ratios of adverse health outcomes against the percentages of women who reported each sleep duration

## 1.4 Assessing Sleep Patterns

### 1.4.1 Gold Standard (PSG)

Sleep is most accurately defined through electroencephalogram (EEG) measurements, combined with electromyography (EMG) and electrooculography (EOG)[4]. Sleep is most often clinically measured through PSG which encompasses EEG, EMG and EOG. The gold standard for objectively measuring sleep and diagnosing sleep disorders is a polysomnogram (PSG). The PSG analysis involves recorded and analyzed measurements of brain function, muscle movement, ocular movement, respiratory function, cardiac rhythm, sleep onset and arousals[25]. A PSG study requires a trained expert to collect the data and to analyze the results, which may not be feasible outside a specialised sleep clinical or research setting.

### 1.4.2 Actigraphy/Accelerometers

Actigraphy is a small, portable device that senses and stores a person's physical motion during sleep and wake cycles[26]. This device can be used to evaluate and research clinical sleep disruptions by generating an internal signal each time the device is moved/accelerated [27]. Actigraphy devices worn on the wrist were first used for the assessment of sleep in 1972[28]. An accelerometer allows the continuous detection of sleep periods in an individual's normal sleep environment and is supported by the Society of Behavioural Sleep Medicine.[26]. Using an accelerometer to objectively measure sleep patterns have been validated for both older adults[29] and in children[30]. Based on population- based studies for sleep analysis, it has been recommended that the accelerometer be worn on the non-dominant wrist. Although actigraphy

should not be viewed as a substitute for PSG to diagnose clinical sleep disorders. However, accelerometers are a recognized tool that can be useful to measure 24-hour movement patterns, including those associated with sleep[26]. It has been demonstrated that there is a 91-93% agreement between PSG sleep parameters and actigraphy device placed on the wrist[31]. Additionally, the Cole Kripke algorithm, correctly distinguished sleep from wakefulness in approximately 88% of minutes scored compared to PSG[29]. Additionally, according to Kelsie et. al., the pattern of SE estimates shows that 57% of SE estimates from the non-dominant wrist-worn accelerometer devices fall within 5% of the mean PSG SE estimates[28]. As well, no significant differences were found in total sleep time using a wrist mounted research-grade accelerometer when compared with the gold standard of polysomnography[28].

### 1.4.3 Pittsburgh sleep quality index

The Pittsburgh Sleep Quality Index (PSQI) is a subjective questionnaire that contains questions that relate to usual sleep habits during a period of one month. The response the participants answered should indicate the most accurate reply for the majority of days and nights in the past month. It includes multiple questions relating to sleep duration and sleep quality which produces a global score that can determine the quality of an individual's sleep. The respondents rate which various factors interfered with their sleep based on a 4-point Likert-type scale. A total score >5, out of a total of 21 points indicate poor sleep quality[20]. The PSQI is a well known research and clinical measurement tool used in epidemiological studies with diverse, older racial or ethnic groups[32]. Beaudrea et al. further validated the use of the PSQI for research and clinical use and demonstrated it is an appropriate tool to use with older women to assess sleep quality[33].

## 1.5 Cardiovascular disease

Cardiovascular disease (CVD) is a general term to describe several different disorders and abnormalities present in the heart or the vascular system. Some of the pathologies that present under the umbrella term of CVD includes coronary heart disease (CHD), peripheral arterial diseases, heart failure and congenital heart diseases[34]. Atherosclerosis is the leading cause of CVD, including both heart diseases and stroke[35]. Atherosclerosis is a progressive disease where lipids and fibrous elements accumulate in the large arteries causing blockages[35]. These blockages can grow sufficiently in the arteries that can complicate the cardiovascular system, such as blocking blood flow due to a blood clot of a thrombus. These blockages can result in life threatening conditions such as myocardial infarction or stroke[35]. CVD is the leading cause of mortality globally[36].

In 2016, the WHO estimated that over 75% of premature CVD was preventable and could be decreased by primary risk factor interventions. Primary interventions should address the effects of CVD risk factors including smoking, hypertension, and obesity. Despite the advances of the care and treatment of CVD, as well as advances in CVD research, the prevalence of CVD is not diminishing. The World Health Organization projects that by 2030 CVD prevalence will be 32%[37]. Research must address this growing problem by finding preventative measures and interventions that can reduce the impact of CVD worldwide.

Hypertension is an important risk factor for both non-fatal and fatal CVD[38]. European Society of Cardiology (ESC) guidelines for the management of hypertension define hypertension as a systolic BP values of >140 mmHG and diastolic BP values of >90 mmHg at rest[39,40]. Hypertension is a global health problem and is the leading cardiovascular risk factor for morbidity and mortality worldwide[38]. According to the WHO, an estimated 1.13 billion people

worldwide have hypertension[41]. Additionally, according to WHO, in 2015 1 in 5 females had hypertension[41]. Its prevalence has increased over the past decade despite improvements in awareness, treatment and control of BP[42]. Although the prevalence of hypertension is greater in men until middle age, women have similar or higher rates of hypertension compared to men later in life[43]. In postmenopausal women, hypertension is the most common modifiable cardiovascular risk factor[43]. In women aged 65 years and older the prevalence of hypertension exceeds 60% and rises to 76.2% in those 75 years or older[43][40]. A combination of genetic and environmental factors have been identified as important in the development of hypertension.

### 1.5.1 Short Sleep and CVD risk

Short sleep duration is associated with the prevalence and incidence of CVD[44]. A meta-analysis that included 15 studies, with a total of 474,684 participants, demonstrated that individuals that self reported as short sleepers ($\leq$6 hours) had a 50% increase in the risk of developing coronary heart disease (CHD)[45]. Yin et al. reported that a reduction in 1-hour of sleep was associated with a 6% increase risk for all-cause mortality and total CVD, a 7% increase risk for CHD and a 5% increase risk for stroke[46,47]. The Helius Study, a large- scale prospective cohort study of 13,316 participants demonstrated that the prevalence of hypertension was consistently higher in those reporting short sleep duration (<6 hours) compared to normal sleepers[48]. Short sleep duration has a potential impact on endocrine function[49], immune system function and inflammatory processes[49].

### 1.5.2 Long Sleep and CVD risk

Long sleep duration ($\geq$9 hours per night) is associated with an overall decrease in health status across multiple domains. Lifestyle factors including poor sleep quality, poor physical and

mental health, anxiety, depression, low socioeconomic status, low level of physical activity and other underlying biological mechanisms[49] have been shown to be present in individuals with long sleep duration. The NHS demonstrated sleeping 9 hours or more was associated with a 42% increased mortality risk, compared to normal sleepers (7-<9 hours)[50].

Another theory for the association between adverse health outcomes and an increased self-reported sleep duration is individuals with long sleep needs may have a reduced physiological reserve, reducing the ability of an individual to survive serious illness[50]. Sleeping >9 hours/night is associated with higher risks of CVD in individuals aged 55 years or older[47]. Cepeda et al. demonstrated that the odds of having CVD was 43% higher in subjects aged 55 years or older who reported sleep >9 hours sleep compared with subjects in the same age category who sleep <6 hours[47]. Yin et al. demonstrated that with a 1-hour increase in sleep duration, compared to 7 hours per night, all-cause mortality risk was increased by 13%, total CVD risk was increased by 12%, CHD was increased by 5% and stroke risk was increased by 18%[46]. Kripke et al. (1979) reported individuals sleeping ten hours or more were about 1.8 times as likely to have died within six years as subjects who reported sleeping 7.0 to 7.9 hours[51].

### 1.5.3 Sleep Quality and CVD risk

Sleep quality is an important behavioural factor associated with CVD outcomes, where low sleep quality is associated with the highest risk for negative health outcomes[52]. The MORGEN study which included 20,432 participants without prevalent CVD based on self-report and hospital admission data demonstrated after age and sex adjustments, participants with poor sleep quality, where sleep quality was assessed using a self-report asking “Do you usually rise rested”, had a 22% higher risk of CVD and 34% higher risk of CHD incidence than those with

good sleep quality[53]. Sleep quality is an important factor for the recovery of the physiology system. Further adverse health outcomes associated with poor sleep quality includes increased risk mortality, type 2 diabetes and obesity[54]. Analysing sleep quality, with sleep duration is important to understand the overall impact that negative sleep patterning can have on the human system

### 1.6 Sleep in Older Aged Females

As individuals advance into older age, total sleep time gradually declines and the total number of awakenings increase during a sleep session[1]. A meta-analysis of 65 studies representing 3,577 healthy subjects has shown that the total amount of sleep decreases linearly with age with a loss of ~10 minutes per decade[55]. Cross-sectional studies have also demonstrated that the prevalence of self-reported poor sleep increases with age[56,57]. For example, the proportion of individuals reporting trouble with sleep increase from 9% at age 2-29 to about 21% at age 60-69[56]. Many studies also indicate the predominance of females in reporting poor sleep. The changes in sleep may be due to aging itself, or due to the contribution of other age related-diseases that may impact sleep[51].

It is apparent from existing research that sleep disturbances are highly prevalent in older adults, where nearly 70% report problems with their sleep, and 32-45% report difficulty falling asleep or maintaining sleep[33]. Both extremely long and extremely short sleep durations were reported by higher percentages of older persons[51]. According to current research, longer sleep duration may put older women at an increased risk of adverse health outcomes including CVD[58].

A prominent change in sleep cycles with ageing occurs in S3 and S4, where there is an overall reduction[3]. The reduction of S3 and S4 could be associated with the occurrence of diseases such as dementia[10,47,59]. Understanding how age and sex is linked to sleep duration needs further investigation. It has been consistently found that women (independent of age), on average, sleep longer than men[46,60]. In the Jean-Louis et al. study, it was demonstrated that women slept 28 minutes longer than men during night sleep[60]. According to the Nurses' Health Study (NHS) cohort of 82,929 women, it was demonstrated that women reporting long sleep duration, equal to or greater than 9 hours of sleep, tended to be older, heavier and have more comorbidities[50].

### 1.7 Sleep and Blood Pressure

In Canada, 22.7% of adults aged 20 years and older are living with hypertension, where approximately 17% of individuals with hypertension are not aware of their condition. Poor sleep patterning is associated with an increased risk for hypertension across the lifespan. Sleep restrictions alter the autonomic balance and increase the sympathetic nervous system activity and circulating levels of catecholamines[61]. Disruptions in time and duration of sleep also impairs circadian rhythmicity and contributes to non-dipping BP patterns and a risk in BP variability. BP and heart rate follow a diurnal pattern with the lowest values occurring during sleep. BP gradually falls with the onset of sleep and then remains low until the moment of awakening, when it promptly rises[42]. BP drops by an average of 10-20% during sleep. Sleep deprivation studies of both normotensive and hypertensive subjects have shown significant increases in BP and sympathetic nervous system activity after nights where sleep was restricted[42].

### 1.8 Exaggerated Blood Pressure Response to Moderate Intensity Physical Activity

Exercise stress testing is routinely used to assess CVD risk through the measurement of BP[62]. When the body is presented with a stressor, such as exercise, it adapts physiologically to meet the needs of the system. The baroreceptor reflex, or baroreflex, is the most important mechanism involved in BP control which responds to changes in carotid or aortic stretch caused by rises or falls in arterial BP[63]. During moderate bouts of physical activity, systolic BP increases and there is little or no change in DBP[43]. SBP normally rises with exercise due to the increase in cardiac output[64]. This is due to the increased demand of oxygen from the working muscles involved in the exercise as well as the increases in metabolic demands of the involved organs[38,43]. Additionally, impaired endothelial function may limit vasodilation in response to increased shear stress from exercise and, therefore, result in an exaggerated blood pressure response (EBPR)[64].

The American Heart Association (AHA) published evidence-based guidelines in 2007 for the evaluation of high blood pressure in adults. It is recommended, prior to measuring BP in a clinical setting, individuals are to be seated and rested for a 5-minute period[65]. Emerging research suggests that the blood pressure response to acute exercise may also have prognostic value in identifying future CVD risk, such as masked hypertension[62,66], future hypertension[66,67] as well as identifying physiological mechanisms, such as autonomic dysfunction which could increase future CVD risk. Individuals with elevated CVD risk, but who are not formally diagnosed with CVDs, may present an abnormally exaggerated BP response to physical activity. In fact, people with abnormally high BP levels during physical activity tend to develop left ventricular hypertrophy and end organ damage[43]. Some studies suggest that the exaggerated systolic BP response is associated with future development of hypertension[64,68].

A previous meta-analysis of 12 longitudinal studies with a total of 46,314 individuals revealed that an EBPR during moderate physical activity increased adverse cardiovascular outcomes (fatal or non-fatal myocardial infarction, stroke, or development of coronary artery disease) by 36 % after adjustment for other cardiovascular risk factors[69].

Approximately 50% of older adults have elevated SBP but relatively normal DBP at rest[70]. Arterial stiffness is associated with the aging process[71]. This can result in structural changes, where arteries are less able to expand in systole and buffer the rise in SBP caused by the increased cardiac output during physical activity[43]. More specifically in older adults, an increase in arterial stiffness can result in a reduction in arterial compliance, which could then lead to an abnormal increase in BP during exercise[64]. An EBPR may be caused by arterial stiffness and autonomic dysfunction, which can not be assessed using resting blood pressure values.

### 1.9 Sleep and Exaggerated Blood Pressure Response

Literature has substantially demonstrated that poor sleep patterning can increase the risk of developing hypertension and CVD. Hypertension is normally measured at rest, but current literature[67,68,72,73] has shown that an EBPR to moderate physical activity may be a more sensitive approach to detect hypertension by challenging the autonomic nervous system for BP regulation. Cardiovascular autonomic dysfunction and disturbed sleep patterns may result from a common pathogenic mechanism. A common mechanism (Figure 3) that may connect poor sleeping patterns to the development of hypertension is that the alterations in sleep patterning leads to the loss of BP dipping during sleep[74]. This loss in BP dipping is mainly attributable to an increase in sympathetic activity during sleep, which leads to an increase in sympathetic tone during the day[74]. Poor sleep patterning negatively influences resting blood pressure[75].

However, no published literature has examined the potential relationship between sleep patterning and an EBPR to moderate intensity exercise.

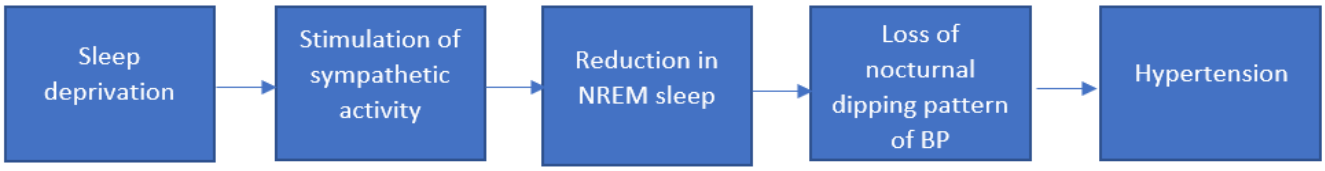



*Figure 3: "Adapted" The common intermediary mechanism for the link between sleep and hypertension*[74]

## Chapter 2: Statement of the Problem and Methods

### 2.1 Statement of the problem

In 2007/2008 the prevalence of hypertension in Canadian women, aged 55 years and older was 59%[76]. Determining pre-clinical CVD risk in an all-female population could be an important contribution to decrease the prevalence of hypertension. Current methods to assess the risk for developing hypertension, according to Hypertension Canada Guidelines, includes measuring BP at rest using a sphygmomanometer. The problem with this approach is that the measure of resting BP may not be sensitive enough to detect pre-clinical CVD risk. Measuring an EBPR to 3-minutes of moderate physical activity, may be more sensitive to detect pre-clinical CVD risk. Moreover, it is known that poor sleep patterning is associated with hypertension in adults, which likely contributes to adverse cardiovascular events. Sleep patterning may have a stronger association with an EBPR than does resting BP, which is a relationship that has been examined substantially in the current literature[52,61,77–79] However, it is not known if poor sleep patterning associates with an EBPR to physical activity in adults. If sleep patterning has a strong association with an EBPR, healthcare professional may be able to assess sleep patterning as an early sign of pre-clinical CVD risk, future cardiovascular complications or adverse events. My thesis examined this knowledge gap.

### 2.2 Thesis Objective and Hypotheses

The main objective of my thesis research was to determine if sleep patterns associate with an EBPR to 3-minutes of moderate physical activity in a cohort of women 55 years of age and older. I hypothesized that:

1. Sleep duration (assessed by accelerometry variable TST and transformed into a categorical variable based on literature cut-offs with levels defined as short sleep

duration, of <7 hrs per night and normal sleep duration of ≥7 hrs to <9 hrs) will be associated with an absolute EBPR of ≥150 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $Typical_{Absolute}$ or $Exaggerated_{Absolute)}$. The hypothesis will then be tested again after controlling for resting blood pressure.

2. In a cohort of women aged 55 years and older, sleep duration (assessed by accelerometry variable TST and transformed into a categorical variable based on literature cut-offs with levels defined as short sleep duration, of <7 hrs per night, compared to normal sleep duration of ≥7 hrs to <9 hrs) will be associated with a relative EBPR of ≥40 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $Typical_{Relative}$ or $Exaggerated_{Relative}$).
3. Sleep duration (assessed by accelerometry variable TST and transformed into a categorical variable based on literature cut-offs with levels defined as normal sleep duration ≥ 7 hours < 9 hours or Long sleep duration ≥ 9 hours) will be associated with an absolute EBPR of ≥150 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $Typical_{Absolute}$ or $Exaggerated_{Absolute}$). The hypothesis will then be tested again after controlling for resting blood pressure.
4. Sleep duration (assessed by accelerometry variable TST and transformed into a categorical variable based on literature cut-offs with levels defined as normal sleep duration ≥ 7 hours < 9 hours or Long sleep duration ≥ 9 hours) will be associated with a relative EBPR of ≥40 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $Typical_{Relative}$ or $Exaggerated_{Relative}$).

- Sleep duration (assessed by accelerometry variable TST and examined as a continuous variable) will be associated with an absolute EBPR of >150 mmHg to 3 minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $\text{Typical}_{\text{Absolute}}$ or $\text{Exaggerated}_{\text{Absolute}}$). The hypothesis will then be tested again after controlling for resting blood pressure.
- Sleep duration (assessed by accelerometry variable TST and examined as a continuous variable) will be associated with a relative EBPR of $\geq$40 mmHg to 30minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $\text{Typical}_{\text{Relative}}$ of $\text{Exaggerated}_{\text{Relative)}}$

5. Sleep Efficiency (SE; assessed by accelerometry and transformed into a categorical variable based on ActiLife cut-offs with levels defined as Poor <85% and Adequate $\geq$85%) will be associated with an absolute EBPR of $\geq$150 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $\text{Typical}_{\text{Absolute}}$ or $\text{Exaggerated}_{\text{Absolute}}$). The hypothesis will then be tested again after controlling for resting blood pressure.
6. Sleep Efficiency (SE; assessed by accelerometry and transformed into a categorical variable based on ActiLife cut-offs with levels defined as Poor <85% and $\geq$85%) will be associated with a relative EBPR of $\geq$40 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $\text{Typical}_{\text{Relative}}$ or $\text{Exaggerated}_{\text{Relative}}$).
    - Sleep Efficiency (SE; assessed by accelerometry and examined as a continuous variable) will be associated with an absolute EBPR of >150 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR

response is either $Typical_{Absolute}$ or $Exaggerated_{Absolute}$). This hypothesis will then be tested again after controlling for resting blood pressure.

- Sleep Efficiency (SE; assessed by accelerometry and examined as a continuous variable) will be associated with an absolute EBPR of $\geq$40 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $Typical_{Relative}$ or $Exaggerated_{Relative}$).

7. Sleep Quality (assessed by PSQI score and transformed into a categorical variable based on literature cut-offs with levels defined as Poor $\geq$5 and Adequate of <5) will be associated with an absolute EBPR of $\geq$150 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $Typical_{Absolute}$ or $Exaggerated_{Absolute}$). This hypothesis will then be tested again after controlling for resting blood pressure.
8. Sleep Quality (assessed by PSQI score and transformed into a categorical variable based on literature cut--offs with levels defined as Poor $\geq$5 and Adequate of <5) will be associated with a relative EBPR of $\geq$40 mmHg to 3-minutes of moderate physical activity (assessed as a categorical variable where EBPR response is either $Typical_{Relative}$ or $Exaggerated_{Relative}$). The hypothesis will then be tested again after controlling for resting blood pressure.

## 2.3 Methods

### 2.3.1 Research design

The comparison of sleep patterns and BP in response to 3-minutes of moderate physical activity in this thesis was performed using a secondary analysis of observational, cross-sectional

cohort data collected from the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts cardiovascular screening project (ClinicalTrials.gov ***NCT03938155)***. The WARM Hearts study was designed to examine a series of CVD risk screening measures and determine if any of the collected measures predict future adverse cardiovascular events 5 years post-screening. The WARM Hearts cohort protocol paper is currently under review for publication. The following sections in this document will briefly describe the methodological approaches that are specific to my thesis research.

The WARM Hearts study received ethical approval from the University of Manitoba Health Research Ethics Board (H2019:063) and the St. Boniface Research Review Committee (RRC/2019/1833). This thesis was developed using The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines[80] (see Appendix 1) and Sex and Gender Equity in Research (SAGER)[81] guidelines (Appendix 2). Bem Sex Role Inventory Short Form from the GENESIS PRAXY study will measure dimensions of masculinity and femininity in the WARM Hearts study. Gender will also be self-reported in the WARM Hearts study. Participants were asked an open-ended question as follows, what is your gender identity? [man, woman, transgender, two spirit or prefer to self-identify (open-ended response)]. Researchers who are interested in the self-reported gender score or the gender score from the Bem Sex Role Inventory Short Form and the self-reported gender identity can contact Dr. Todd Duhamel to request access to the data. The full cohort of 206 used for this analysis identified as women.

The WARM Hearts study will recruit one-thousand female participants, 55 years of age or older through convenience sampling. An all-female cohort was recruited because CVD is the number one killer in women[82]. The relative risk in females of CVD morbidity and mortality is

higher than males[83]. CVD develops 7-10 years later in women than in men[84], with an equal prevalence rate in women and men by age 40[85].This is most likely due to the protective effects of estrogen pre-menopause[82]. The older age at onset of CVD has left females underrepresented due to the lower prevalence rates in younger age groups. Historically, females are under-represented in CVD research and clinical trials[86]. This may affect a female's ability to receive proper prognosis and treatment due to the differences in clinical presentation of CVD compared to males. The impacts from CVD in terms of disability is staggering where about 36% of women aged 55-64 years, and 55% of women aged 75 years and older have major disabilities after a myocardial infarction[43]. The discrepancies in the presentation and outcomes between sexes are associated with inequalities in the detection, prevention and management of CVD[87].

The recruitment of the cohort used newspaper ads, media advertising and radio interviews. Women who were interested in participating in the study were instructed to contact the WARM Hearts research team by telephone or email. The inclusion and exclusion criteria for the WARM Hearts are described in Table 2. If a woman was deemed eligible and interested in participating in the study, they were then be booked into their first appointments at the (1) Active Living Centre, University of Manitoba, and then their second appointment at the (2) I.H. Asper Clincial Research Institute. At the first appointment written consent was obtained (Appendix 3). Recruitment for the WARM Hearts study began in October 10, 2019. The WARM Hearts study began collecting data on October 10$^{th}$, 2019 and as of March 23$^{rd}$, 2020 four hundred and eighty (480) individuals were recruited to participate. Of these individuals, a total of 240 completed data collection. Due to the COVID-19 public health pandemic, the WARM Hearts study discontinued the recruitment and data collection from human participants past the date of March 23$^{rd}$, 2020. Recruitment and data collection will recommence when public health authorities

indicate it is safe to do so. For this thesis research, a total of 206 women from the WARM Hearts cohort will be used for analysis.

**Table 2:** Inclusion and exclusion criteria for the WARM Hearts study

| **Inclusion criteria** |
| --- |
| • **Women aged 55 and older**<br>• **Possess a Manitoba Personal Health Information Number** |
| **Exclusion criteria** |
| • **Ischemic heart disease**<br>• **Acute myocardial infarction**<br>• **Stroke**<br>• **Percutaneous coronary intervention**<br>• **Coronary artery bypass surgery**<br>• **Congestive heart failure**<br>• **Peripheral artery disease**<br>• **Previous participation in The Assessment of Large and Small Artery Elasticity for the Early Detection of Cardiovascular Disease study**[88] |

## Measurements

*Activity Log*

The participants were given an Activity Monitor Log which included written instructions for the wearing and use of the accelerometer. This booklet instructed the participants to record the specific time of day, to the nearest minute for 1) “Wake time”, defined as the time you first

woke up; 2) “Time you got out of bed” defined as the time when you physically got out of bed; 3) “Bed time” defined as the time you got in bed; and 4) “Time you fell asleep” defined as the time the participants think they actually feel asleep. The participants were instructed to record if they removed the accelerometer device at any period throughout the 7 days and indicate the reasoning. Comments could include bathing, showering, and swimming as the monitors are not water-resistant. The participants were instructed to record any naps they had throughout the 24-hour period over the full 7 days. The Activity Monitor Log was only used to assist in the interpretation and analysis of sleep data captured with the accelerometer.

*Sleep analysis by 7-day actigraphy*

Objective measures of poor sleep has been quantified largely using actigraphy in population-based studies to characterize indicators of sleep and activity parameters[32]. Participants were sent home with an accelerometer and instructed to wear the device for 7 consecutive days on their non-dominant wrist for the full 24 hours per day. Eight to 14 days later, the participants returned the device to the research team at their second appointment. Wrist worn actigraphy is a superior method for assessing sleep, compared to hip worn actigraphy for measuring sleep[89]. For example, Zinkhan et al. found wrist worn accelerometers performed better in assessing TST and SE parameters than hip-worn accelerometers when compared to PSG. Further, previous sleep actigraphy validation studies have placed the accelerometer on the non-dominant wrist[21,28,89,90].

The sleep measures were calculated from raw actigraph data for each unit and stored in epochs, which can range from 1 second to 5 minutes. The most validated and commonly used epoch lengths for sleep are 30 seconds and 60 seconds[26]. The WARM Hearts study analyzed the accelerometer data with a 60 second epoch length. Appendix 4 is the standardized operating

procedures used to analyse the sleep data of each participant in the WARM Hearts study. Actigraphy recordings were performed using GT3X+ activity monitors. Wrist actigraphy data was downloaded and analysed using the ActiLife software (Version 6.13.4). The selection of the algorithm used to assess sleep is dependent on the age of the participants. Since the participants in WARM Hearts are females, aged 55 years or older, the Cole-Kripke Algorithm was used to analyze sleep patterns as it has been used in studies for adults over the age of 30[29]. The Cole-Kripke algorithm, built into the ActiLife software, was applied to the identified primary sleep periods, and classified each minute of the sleep period as "sleep" or "wake". The algorithm calculates a movement average, which considers the activity level immediately prior to and after the current minute to determine if each timepoint should be coded as sleep or wake. Estimates of nightly sleep duration was derived from the summing of epochs classified as sleep by the Cole-Kripke algorithm (minutes/night) during the defined primary sleep period. The Cole-Kripke sleep algorithm was developed using the wrist worn accelerometers [29] and the placement is supported by the Society of Behavioural Sleep Medicine (105). Using the Cole-Kripke algorithm the participants sleep patterning was analysed by inputting the "In Bed Date", "In Bedtime, "Out Bed Date" and "Out Bedtime" for each of the 7 individual days that the participant wore the actigraphy device (Appendix 4). Two separate files were created. The first file was the day to day analysis of sleep; whereas, the second file was an average of the 7 days of data. The average of the 7-day file was used to create the sleep quality and sleep duration variable.

Sleep duration was assessed by TST a sleep parameter determined by the minutes of sleep between "lights off" and "lights on" or the duration of sleep during the major sleep period[26]. TST was first analysed using the Cole Kripke Algorithm which predetermined times for "lights off" and "lights on" based on the algorithms coding, with a wear time of at least 80%.

This was then checked with the values provided on the Activity Monitor Log that participant filled out for the 7-days of sleep recording to ensure that the ActiLife system had correctly distinguished TST. The “lights off” and “lights on” were manually entered into the ActiLife software based on the participants Activity Monitor Log information that the participants filled out during the 7-day period if the values initially provided from the algorithm were incorrect. Additionally, naps during the day were removed from the analysis, which may had been coded as nighttime sleep from the Cole-Kripke algorithm

SE, an actigraphy sleep parameter, was analysed to assess sleep quality. This sleep parameter is a good indicator for sleep quality and is obtained by dividing TST by total bedtime and then multiplying by 100 to obtain a percentage[91]. Poor sleep quality was determined by a percentage efficiency below 85%, which is a common cut-off value implied in making the diagnosis of insomnia in adults[24].

*Pittsburgh Sleep Quality Index*

Participants were instructed to fill out a series of questionnaires. For the analysis of the subjective sleep quality parameter, the total global score was determined. PSQI is a validated questionnaire in community-dwelling older, diverse women [32]. The PSQI assesses the participants usual sleep habits during the past month. The participants were instructed to fill out this questionnaire and return it at the second and final appointment.

*Resting Blood Pressure*

At the scheduled second appointment resting/baseline BP was measured in accordance to AHA guidelines and Hypertension Canada’s guidelines[65,92]. A BP cuff was attached to the Mobil-O-Graph[93] and was placed on the participant’s arm, with an appropriate cuff size, while

seated [65]. Two numbers were recorded when measuring resting BP. The higher number of the two is systolic BP which represents the pressure in the heart when the left ventricle of the heart is contracting. The lower number represents diastolic BP which represents the pressure in the heart when the left ventricle is filling with blood.[94] BP was measured in millimeters of mercury (mmHg) and recorded with the systolic number first, followed by the diastolic number. According to the Hypertension Canada's (2018) Guidelines[92], for BP values are as followed.

1. A BP value of 120/80 mmHg or less is considered normal in adults
2. A BP value of 120-139/80-89 mmHg is considered pre-hypertensive, potentially indicating a development of future high blood pressure (hypertension)
3. A blood BP value of 140/90 mmHg or higher is classified as high BP and is considered to increase your risk for cardiovascular and health complications.

*Exaggerated blood pressure response to moderate intensity exercise*

The magnitude of the rise in BP during exercise may be an indication of early risk for developing hypertension, even if the participant's resting BP is normal[66]. After the resting BP was assessed, the participants were asked to perform 3 minutes of moderate exercise on a treadmill at 4.8 km/h at 4% grade or 4 km/h at 6% grade, whatever the participant is able to complete. Both are equivalent to 5 MET workload which is defined as a moderate intensity workload. After the completion of the 3-minutes of moderate physical activity performed on a treadmill, blood pressure was immediately taken (within 30 seconds) in a seated position. An EBPR will be determined using previously published cut-off points. Researchers have chosen to define an EBPR by absolute and relative levels of BP achieved after exercise[66]. Currently, there is insufficient data to denote a definitive absolute and relative cut-off point regarding an

EBPR. However, a previous study has demonstrated a positive association between submaximal intensity exercise with an absolute systolic BP ≥150mmHg and hypertension[72]. The absolute level of BP will be based on Schultz et al. (2016)[72] previous study. Additionally, according to Sharman et al. (2015)[95], a normal relative SBP response is a rise that approximates 10 mmHg (plus-or-minus-two) per MET. During the Bruce treadmill protocol, a normal SBP response to the first stage, which is equivalent to 5 METs, of the test is generally 28mmHg for women[96]. For this thesis, a relative EBPR will be ≥40mmHg as the relative change from rest (1MET) to the moderate intensity physical activity performed (5 METs) is 4 METs.

## 2.4 Statistics

Sleep duration assessed by TST (Sleep duration$_{TST)}$ was divided into three groups; 1) normal sleep duration assessed by TST (normal sleep duration$_{TST)}$; 2) short sleep duration assessed by TST (short sleep duration$_{TST)}$, and; 3) long sleep duration assessed by TST (long sleep duration$_{TST)}$. Since well established cut-offs of short and long sleep duration$_{TST}$ do not exist, I defined sleep duration$_{TST}$ as a categorical variable. Sleep duration$_{TST}$ was coded in categories of, <7 hours, ≥7-<9hrs, ≥9hrs. Sleep duration$_{TST}$ was also be analysed as a continuous variable (Sleep duration$_{continuous}$). For the blood pressure response category groups, an exaggerated absolute blood pressure response (EBPR$_{Absolute)}$ will be defined as ≥150 mmHg compared to the typical absolute blood pressure response (typical$_{absolute)}$ (<150 mmHg). An exaggerated relative blood pressure response (EBPR$_{relative)}$ was defined as ≥40 mmHg compared to the typical relative blood pressure response (typical$_{relative)}$ (<40 mmHg). To compare the differences between binary variables without the contribution of confounding variables, a chi-square test (for categorical variables) was utilized. For analysis, a chi-square was used to assess the relationship (2X2) between short sleep duration$_{TST}$ and normal sleep duration$_{TST}$ against the

blood pressure response category to 3 minutes of moderate physical activity, categorized as both absolute and relative blood pressure response category. Long sleep duration$_{TST}$ was not be included in the research study analysis because it is underpowered based on the 206 cohort. The original plan was to assess short sleep duration$_{TST}$ and long sleep duration$_{TST}$ separately, compared to normal sleep duration$_{TST}$. This approach was going to be used because current research has hypothesised that short and long sleep are potentially different risk factors mediated by separate pathways[49]. The strength of the relationship between these variables were assessed using a Phi coefficient. Additionally, sleep duration$_{TST}$ was assessed as a continuous variable in a binary logistic regression to identify the association between sleep duration$_{continuous}$ and both absolute and relative blood pressure response to 3-minutes of moderate physical activity.

Sleep quality was assessed using both objective and subjective assessment tools. The objective sleep quality was based on SE (Sleep Quality$_{SE}$), assessed by the ActiLife software and coded either ≥85%, indicating adequate sleep Quality$_{SE}$, or <85% indicating poor sleep Quality$_{SE}$. Due to the small sample size representing poor sleep Quality$_{SE}$, SE was assessed SE$_{continuous}$. To assess SE$_{continuous}$, a logistic regression model was used.

Subjective sleep quality was assessed based on PSQI score (Sleep Quality$_{PSQI}$). Sleep Quality$_{PSQI}$ score was categorically coded as either ≥5, indicating poor sleep quality, or <5, indicating adequate sleep quality. A chi-square was used to assess the relationship between sleep quality$_{PSQI}$ and the blood pressure response category. To assess the strength of association, a Phi coefficient was used for the above, 2x2 variables.

A binary logistic regression model was used to predict an EBPR$_{Absolute}$ while controlling for resting systolic blood pressure. The binary logistic regression for EBPR$_{relative}$ did not include controlling for resting systolic blood pressure since EBPR$_{relative}$ value is calculated by taking the

difference between resting systolic blood pressure and systolic blood pressure post the 3 minutes of moderate physical activity. To be included in the analysis for objective sleep variables, seven nights of wear will be required. For all analyses, statistical significance was defined as a 2-tailed P-value < 0.05. All analyses were conducted using SPSS software.

A subset of the WARM Hearts study participants had their sleep patterning and an EBPR assessed. This study consists of 206 individuals. This sample allowed for a 20% difference in the rate of an EBPR to be detected between those with poor and normal sleep pattering with a two-tailed alpha of 0.05 and at a power of 80%.

***Feasibility and potential pitfalls due to COVID-19***

The global COVID 19 pandemic caused research in Manitoba to be paused as of March 24$^{th}$, 2020. The resulting impact of that research pause was that it limited the number of participants data that I could access from the WARM Hearts cohort. Therefore, my thesis examined data from the 206 participants who had valid sleep and BP response to physical activity data collected prior to March 24$^{th}$, 2020.

# Chapter 3: Results

## 3.1 Overall Cohort Participant Characteristics

Two-hundred and six (206) females had valid data and were included in the cohort. The mean age of the cohort was 64 ± 6 years, where 87 participants were 65 years or older, with a mean BMI of 26 ± 5.0 kg/m$^2$; while, 100% of the cohort identified as a women. Participants who lived alone accounted for 16.5% of the cohort and participants who had completed post-secondary education composed 79.6% of the cohort. Ex or current smokers composed of 48.5% of the cohort. The mean age of menopause onset was 50 ± 5.3 years in the cohort of 206 females. The mean systolic blood pressure prior to the 3-minutes of the moderate physical activity was 119 ± 13 mmHg, and resting heart rate of 73 ± 14 bpm. The mean relative post-exercise blood pressure response was 23 ±17 mmHg, and the absolute mean was 142 ± 23 mmHg. The mean HDL cholesterol was 1.72 ± 0.43, the mean LDL cholesterol level was 3.50 ± 0.90 and total cholesterol was 5.24 ± 0.90. For this cohort, the mean Framingham Risk Score (FRS) 10-year risk was 6.64 ± 4.13 which indicates a low CVD risk.

The mean for sleep duration based on TST calculated by ActiLife was 7.20 ± 0.92 hrs per night and the mean sleep efficiency value was 91.6% ± 3.5. Based off of the subjective PSQI question, which asked “During the past month, how many hours of actual sleep did you get per night?”, the mean sleep duration was 6.98 ± 1.12 hrs/night. The mean PSQI score was 6.50 ± 3.42 for the cohort of 206 participants. Baseline characteristics for the overall cohort are included in Table 3.

**Table 3:** Baseline Characteristics

| **Characteristics** | **Total Cohort** (n=206) |
|---|---|
| Age (years) | 64 ± 6 |
| ≥65 years old, n (%) | 87 (42.2%) |
| BMI ($kg/m^2$) | 26 ± 5 |
| Gender identity (woman) | 206 (100%) |
| Living alone, n (%) | 34 (16.5%) |
| PS education, n (%) | 164 (79.6%) |
| Ex/Current Smoker, n (%) | 100 (48.5%) |
| Menopause onset (years) | 50.3 ± 5.3 |
| Resting systolic blood pressure (mmHg) | 119 ± 13 |
| Resting heart rate PA (bpm) | 73 ± 14 |
| Relative PA blood pressure response (mmHg) | 23 ± 17 |
| Absolute PA blood pressure response (mmHg) | 142 ± 23 |
| HDL cholesterol (mmol/L) | 1.72 ± 0.43 |
| LDL cholesterol (mmol/L) | 3.50 ± 0.90 |
| Total cholesterol (mmol/L) | 5.24 ± 0.90 |
| FRS 10-year risk (%) | 6.64 ± 4.13 |
| TST (hours) | 7.20 ± 0.92 |
| Sleep Efficiency (%) | 91.6% ±3.49 |
| Subjective TST (PSQI, hrs/night) | 6.98 ± 1.12 |
| PSQI score | 6.50 ±3.42 |
| Poor quality PSQI cut-off, n (%) | 118 (57.3%) |

*Continuous variables expressed as Mean ± standard deviation Categorical Variables expressed as n (%).* ***BMI****, Body Mass Index;* ***PS****, Post-secondary;* ***BP****, Blood pressure;* ***PA****, Physical Activity;* ***FRS****, Framingham Risk Score;* ***TST****, Total Sleep Time;* ***PSQI****, Pittsburgh Sleep Quality Index*

### 3.2.1 Sleep Duration$_{TST}$ and Absolute Blood Pressure Category

In order to test hypotheses 1-4, I divided the cohort into three groups; namely (1) short sleep duration defined as using accelerometer TST data; (2) normal sleep duration of ≥7 hrs to <9 hrs/night and (3) long sleep duration defined as ≥ 9 hrs/night. Using previous research-based cut-off values for sleep duration (TST)[22], the prevalence of short sleepers (<7 hrs/night) in the cohort was 40.8%; whereas, 57.3% of the cohort were classified as normal sleepers (≥7 hrs to <9 hrs/night) and 1.9% were classified as long sleepers (≥9 hrs/night).

To test hypothesis 1, I utilized the groups (1) short sleep duration$_{TST}$, defined as <7 hrs/night using accelerometer TST data; and (2) normal sleep duration$_{TST}$, defined as ≥7 hrs to <9 hrs/night. Table 4 describes the demographic information for the short and normal sleep duration$_{TST}$ groups. This analysis included a total of 202 participants out of the 206, as 4 participants were classified as long sleepers and were removed from this analysis comparing short and normal sleep duration. T-tests were then used to examine differences in mean estimates of age, BMI, heart rate post moderate exercise, menopause onset, resting systolic blood pressure, post-secondary education, living arrangements, smoking status, HDL, LDL and total cholesterol, and FRS 10-year risk score. No significant differences were identified between groups for BMI, heart rate post-moderate exercise, menopause onset, post-secondary education, living arrangements, smoking status, HDL, LDL, total cholesterol or FRS 10-year risk score. However, there was a significant difference between short and normal sleep duration$_{TST}$ groups for age (p=.048) where the short sleep duration$_{TST}$ group was older compared to the normal sleep duration$_{TST}$ group.

**Table 4.** Participant Characteristics for Short and Normal Sleep Duration

| | Sleep Duration | | |
|---|---|---|---|
| Participant Characteristics | Short Sleep Duration | Normal Sleep Duration | P value |
| n (%) | 84 (41.6%) | 118 (58.4%) | |
| Age, years | 63 ± 5.9 | 64 ± 5.9 | .048* |
| BMI, kg/m$^2$ | 26.2 ± 4.8 | 25.8 ± 5.2 | .571 |
| Heart rate post-moderate exercise, bpm | 74 ± 14.6 | 73 ± 13.6 | .651 |
| Menopause onset, years | 51 ± 3.9 | 50 ± 5.9 | .344 |
| Resting systolic blood pressure, mmHg | 118 ± 12.1 | 119 ± 13.9 | .569 |
| Post-secondary education, n (%) | 75 (89.3%) | 113 (95.8%) | .152 |
| Living arrangement (alone), n (%) | 13 (15.5%) | 20 (16.9%) | .781 |
| Ex/current smoker, n (%) | 39 (46.4%) | 60 (50.8%) | .538 |
| HDL cholesterol | 1.65 ± 0.46 | 1.77 ± 0.41 | .053 |
| LDL cholesterol | 3.60 ± 0.92 | 3.41 ± 0.88 | .140 |
| Total cholesterol | 5.27 ± 0.93 | 5.19 ± 0.88 | .565 |
| FRS 10-year risk | 6.54 ± 3.97 | 6.49 ± 3.95 | .925 |
| *Continuous variables expressed as Mean ± standard deviation. Categorical variables expressed as frequency (percentage). Sample size= 202* | | | |

Next, the cohort was divided into two groups based on those participants who presented with either: (1) a Typical$_{Absolute}$ blood pressure response to three minutes of moderate physical activity; or (2) an EBPR$_{Absolute}$ to three minutes of moderate physical activity. Of the 206 participants from the full cohort, 134 (65%) participants had a Typical$_{Absolute}$ blood pressure response, where 72 (35%) participants had an EBPR$_{Absolute}$.

Four groups were created based on the two variable of sleep duration$_{TST}$ and absolute blood pressure response. Specifically, the groups were: (1) short sleeper duration$_{TST}$ with a Typical$_{Absolute}$ blood pressure response; (2) short sleep duration$_{TST}$ with an EBPR$_{Absolute}$; (3) normal sleep duration$_{TST}$ with a Typical$_{Absolute}$ blood pressure response; and (4) normal sleep duration$_{TST}$ with an EBPR$_{Absolute}$. For the four groups created (Table 5), the demographic continuous variable data

was explored by a 2-way ANOVA. The ANOVA identified a main effect between $Typical_{Absolute}$ and $EBPR_{Absolute}$ for age (p=.002), where the $EBPR_{Absolute}$ group were older than the $Typical_{Absolute}$ blood pressure group. The ANOVA also identified a main effect for HR post PA (p=≤.001, BMI (p=≤.001) and AVG RBP (p=≤.001), where the HR post PA, BMI and Avg RBP was higher compared to the $Typical_{Absolute}$ blood pressure group. The sample used for the 2-way ANOVA, which assessed the demographic data of the four groups included 202 participants. This sample excluded the four participants who were classified as long sleepers.

The demographic categorical variable data, such as PS education, tobacco use and living arrangements was explored by a chi-square analysis (Table 5). The sample used for the chi-square analysis which assessed demographic data of the four groups included the 202 participants. This sample excluded the four participants who were classified as long sleepers. No differences were identified for PS education, living arrangements and tobacco use.

**Table 5.** Participant Characteristics for CVD Risk (Absolute) and Sleep Duration Groups

| | Typical$_{Absolute}$ blood pressure response group & Short sleep duration$_{TST}$ | Typical$_{Absolute}$ blood pressure response group & normal sleep duration$_{TST}$ | EBPR$_{Absolute}$ group & short sleep duration$_{TST}$ | EBPR$_{Absolute}$ group & normal sleep duration$_{TST}$ | Main effect of EBPR$_{Absolute}$ P value | Main effect of sleep duration$_{TST}$ P value | Interaction P value | Chi-square P value |
|---|---|---|---|---|---|---|---|---|
| **N (%)** | 57 (28.2%) | 76 (37.6%) | 27 (13.4%) | 42 (20.8%) | | | | |
| **Age, years** | 61 ± 5 | 64 ± 6 | 66 ± 6 | 65 ± 6 | .002* | .182 | .147 | |
| **HR Post PA (bpm)** | 72 ± 15 | 70 ± 12 | 79 ± 14 | 78 ± 14 | ≤.001* | .636 | .770 | |
| **PS education, n (%)** | 50 (88%) | 73 (96%) | 25 (93%) | 40 (95%) | | | | .439 |
| **Living arrangement (Alone), n (%)** | 7 (12%) | 13 (17%) | 6 (22%) | 7 (17%) | | | | .704 |
| **Tobacco use (ex/current), n (%)** | 24 (42%) | 39 (51%) | 15 (56%) | 21 (50%) | | | | .631 |
| **BMI, kg/m$^2$** | 25.6 ± 4.2 | 24.1 ± 3.4 | 27.6 ± 5.7 | 28.9 ± 6.5 | ≤.000* | .912 | .055 | |
| **Menopause onset, years** | 51 ± 4 | 50 ± 6 | 51 ± 4 | 51 ± 5 | .718 | .446 | .652 | |
| **Avg RBP, mmHg** | 114 ± 11 | 113 ± 11 | 127 ± 11 | 130 ± 13 | ≤.001* | .473 | .237 | |
| **denotes statistical significance. Abbreviation: HR, Heart Rate; PA, Physical Activity; PS, Post-secondary; BMI, Body Mass Index; Avg, Average; RBP, Resting Blood Pressure. Sample size 202.* | | | | | | | | |

After exploring the demographic characteristics of the four groups, a chi-square test was then used to assess the association between sleep duration$_{TST}$ and an EBPR$_{Absolute}$ of ≥150 mmHg (Table 6). The chi-square did not identify differences in the frequency of distribution between any of the four groups.

**Table 6.** Frequency Distribution of Absolute Blood Pressure Response and Sleep Duration$_{TST}$

| | Typical$_{Absolute}$ blood pressure response | EBPR$_{Absolute}$ | P Value[a] |
|---|---|---|---|
| **TST (Literature)** | | | |
| <7hrs | 57 | 27 | .610 |
| ≥7hrs-<9hrs | 76 | 42 | |
| *[a]Chi-square P values comparing the distribution between typical absolute blood pressure response and exaggerated absolute blood pressure response. Total sample size 202* | | | |

The second method used to assess the association between sleep duration$_{TST}$ and an EBPR$_{Absolute}$ was a logistic regression analysis (Table 7). The logistic regression was used to predict the risk of having exaggerated blood pressure response based on observed sleep duration$_{TST}$ (short sleep duration$_{TST}$ vs. normal sleep duration$_{TST}$) characteristics. The unadjusted logistic regression model was not significant. The logistic regression model was then adjusted to control for Avg RBP. The logistic regression model controlling for Avg RBP did not identify a statistically significant odds ratio for sleep duration$_{TST}$. Avg RBP was significant where the odds of having an EBPR$_{Absolute}$ was 1.128 (1.089-1.170) higher compared to having a typical absolute blood pressure response.

**Table 7:** Logistic Regression Models with Absolute Blood Pressure Response and Sleep Duration$_{TST}$

| Outcome Variable | | Absolute Blood Pressure Response | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate** | | | | |
| Sleep duration$_{TST}$ (short vs normal) | -.154 | .857 | .474-1.551 | .610 |
| **Multivariate** | | | | |
| Sleep duration$_{TST}$ (short vs normal) | .049 | 1.050 | .516-2.138 | .893 |
| Average RBP | .121 | 1.128 | 1.089-1.170 | .000* |
| **denotes statistical significance. OR, Odds Ratio; RBP, Resting Blood Pressure; TST, Total Sleep Time* | | | | |

Hypothesis 1 was rejected, as both the chi-square and logistic regression statistical approaches found no association between sleep duration$_{TST}$ (short vs normal sleep duration$_{TST}$) and an EBPR$_{Absolute}$ in the cohort of females aged 55 years and older. When Avg RBP was controlled for in the logistic regression model, there was also no association between the Sleep duration$_{TST}$ and the EBPR$_{Absolute}$ in a cohort of females 55 years or older.

3.2.2 Sleep Duration$_{TST}$ and Relative Blood Pressure Category

Using the same approach described for hypothesis 1, sleep duration$_{TST}$ was divided into three groups; namely (1) short sleep duration$_{TST}$ defined as <7 hrs/night using accelerometer TST data; (2) normal sleep duration$_{TST}$ of ≥7 hrs to <9 hrs/night and (3) long sleep duration$_{TST}$ defined as ≥9 hrs/night. In order to test hypothesis 2, two of the groups were utilized; namely (1) short sleep duration$_{TST}$ defined as <7 hrs/night using accelerometer TST data; and (2) normal sleep duration$_{TST}$ of ≥7 hrs to <9 hrs/night. Table 4 describes the demographic information for the short and normal sleepers.

The cohort of 206 participants was also divided into two groups based on relative blood pressure response group category of (1) Typical$_{Relative}$ blood pressure response to three minutes of moderate physical activity; and (2) EBPR$_{Relative}$ to three minutes of moderate physical activity. Of the 206 of the full cohort, 177 (85.9%) had a Typical$_{Relative}$ blood pressure response, where 29 participants (14.1%) had an EBPR$_{Relative}$.

Four groups were created based on the two variable of sleep duration$_{TST}$ and absolute blood pressure response were (1) short sleep duration$_{TST}$ with a typical$_{relative}$ blood pressure response; (2) short sleep duration$_{TST}$ with an EBPR$_{relative}$; (3) normal sleep duration$_{TST}$ with a typical$_{relative}$ blood pressure response; and (4) normal sleep duration$_{TST}$ with an EBPR$_{relative}$. For the four groups

created (Table 8), the demographic continuous variable data was explored by a 2-way ANOVA. There was a significant difference for the main effect between $typical_{relative}$ and $EBPR_{relative}$ for age (p=.002), and BMI (p=.004). The $EBPR_{Relative}$ group were older and had a higher BMI compared to the $Typical_{Relative}$ group. The sample used for the 2-way ANOVA, which assessed the demographic data of the four groups included 202 participants. This sample excluded the four participants who were classified as long sleepers.

The demographic categorical variable data, such as PS education, tobacco use and living arrangements was explored by a chi-square analysis (Table 8). The sample used for the chi-square analysis which assessed demographic data of the four groups included 202 participants. This sample excluded the four participants who were classified as long sleepers. No differences were identified for PS education, living arrangements and tobacco use.

**Table 8.** Participant Characteristics for CVD Risk (Relative) and Sleep Duration Groups

| | $Typical_{relative}$ blood pressure response & Short sleep $duration_{TST}$ | $Typical_{relative}$ blood pressure response & normal sleep $duration_{TST}$ | $EBPR_{Relative}$ & short sleep $duration_{TST}$ | $EBPR_{Relative}$ & normal sleep $duration_{TST}$ | $EBPR_{Relative}$ P value | Sleep $duration_{TST}$ P value | Interaction P value | Chi-square P value |
|---|---|---|---|---|---|---|---|---|
| N (%) | 70 (34.7%) | 104 (50.0%) | 14 (6.9%) | 14 (6.9%) | | | | |
| Age, years | 68 ± 7 | 66 ± 6 | 62 ± 5 | 64 ± 6 | .002* | .751 | .079 | |
| HR Post PA, bpm | 76 ± 15 | 78 ± 12 | 74 ± 15 | 72 ± 14 | .150 | .932 | .642 | |
| PS education, n (%) | 63 (90%) | 100 (96%) | 12 (86%) | 13 (93%) | | | | .366 |
| Living arrangement (Alone), n (%) | 8 (11%) | 18 (17%) | 5 (36%) | 2 (14%) | | | | .158 |
| Tobacco use (ex/current), n (%) | 32 (46%) | 52 (50%) | 7 (50%) | 8 (57%) | | | | .868 |
| BMI, $kg/m^2$ | 25.7 ± 4.4 | 25.5 ± 4.8 | 28.6 ± 6.0 | 28.5 ± 7.4 | .004* | .842 | .930 | |
| Menopause onset, years | 51 ± 4 | 50 ± 6 | 51 ± 4 | 50 ± 5 | .897 | .411 | .876 | |
| Avg RBP, mmHg | 118 ± 13 | 119 ± 13 | 122 ± 10 | 124 ± 18 | .103 | .594 | .939 | |

**denotes statistical significance. Abbreviation: HR, Heart Rate; PA, Physical Activity; PS, Post-secondary; BMI, Body Mass Index; Avg, Average; RBP, Resting Blood Pressure. Sample size 202.*

After exploring the characteristics of the four groups, a chi-square test was then used to assess the association between Sleep $duration_{TST}$ and an $EBPR_{relative}$ of ≥150 mmHg (Table 9). The chi square test did not identify significant differences between any of the four groups.

**Table 9.** Frequency Distributions of Relative Blood Pressure and Sleep $Duration_{TST}$

| | $Typical_{relative}$ blood pressure response | $EBPR_{Relative}$ | P Value[a] |
|---|---|---|---|
| **TST (Literature)** | | | |
| <7hrs | 70 | 14 | .330 |
| ≥7hrs-<9hrs | 104 | 14 | |

*[a]Chi-square P values comparing the distribution between typical relative blood pressure response and exaggerated relative blood pressure response. Sample size (202)*

The second method used to assess the association between sleep duration$_{TST}$ and an EBPR$_{relative}$ was a logistic regression analysis (Table 10). The univariate logistic regression model did not detect statistically significant odds ratio for unadjusted sleep duration$_{TST}$ (short and normal sleep duration$_{TST}$). The association between sleep duration$_{TST}$ and an EBPR$_{relative}$ was not included in a multivariate logistic regression controlling for Avg RBP since the relative blood pressure category group was calculated based on the difference between resting systolic blood pressure prior 3-minutes to moderate physical activity and the post-moderate physical activity systolic blood pressure.

**Table 10:** Logistic Regression Model with the Relative Blood Pressure Response Group

| Outcome | Relative Blood Pressure Response | | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate** | | | | |
| Sleep duration$_{TST}$ (shortvsnormal) | .396 | 1.486 | .667-3.308 | .332 |
| **denotes statistical significance. OR, Odds Ratio; TST, Total Sleep Time* | | | | |

Hypothesis 2 was rejected, as both the chi-square and logistic regression statistical approaches found no association between sleep duration$_{TST}$ (short vs normal sleep duration$_{TST}$) and an EBPR$_{Relative}$ in the cohort of females aged 55 years and older.

3.3.1 Sleep Duration$_{TST}$ (Normal & Long Sleep Duration) Absolute and Relative Blood Pressure Category

In order to test hypothesis 3 and 4, I utilized the groups (1) normal sleep duration$_{TST}$ of ≥7 hrs to <9 hrs/night; and (2) long sleep duration$_{TST}$ of ≥9 hrs/night. Due to the COVID-19 pandemic,

I was unable to recruit the 400 participants that I had originally planned to include in the analysis; rather, a cohort of 206 participants was analyzed. Participants who were classified as Long sleep duration$_{TST}$ which accounted for only 1.9% of the cohort. Statistical testing was underpowered for hypothesis 3 and 4. As a result, they were not examined in my thesis. Hypotheses 3 and 4 will be examined at a future time using the full 1000 participants from the overall WARM Hearts trial after its completion.

### 3.4.1 TST$_{continuous}$ and Absolute Blood Pressure Category

Analyses that were identified after the writing of my thesis proposal were developed and will be addressed in the following section. In the first analysis, I used TST as a continuous variable (TST$_{continuous}$), which is a similar approach found in Full et al.[19] The mean TST for this cohort was 7.20 ± 0.92 hrs/night. The cohort was divided into two groups based on absolute blood pressure response category (1) Typical$_{Absolute}$ blood pressure response to three minutes of moderate physical activity; and (2) EBPR$_{Absolute}$ to three minutes of moderate physical activity.

The method used to assess the association between TST$_{continuous}$ and an EBPR$_{Absolute}$ was a logistic regression analysis (Table 11). In the univariate logistic regression model, TST$_{continuous}$ did not have statistically significant odds ratio. In the multivariate model, TST$_{continuous}$ after controlling for Avg RBP did also not have statistically significant odds ratios. Avg RBP was found to be statistically significant where the odds were of having an EBPR$_{relative}$ were 1.132 (CI±1.092-1.173) higher when the average RBP was higher prior to the moderate bout of physical activity.

**Table 11:** Logistic Regression Models with Absolute Blood Pressure Response Category and $TST_{continuous}$

| Outcome | Absolute Blood Pressure Response | | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate model** | | | | |
| $TST_{continuous}$ | -.025 | .975 | .714-1.332 | .874 |
| **Multivariate model** | | | | |
| $TST_{continuous}$ | -.086 | .918 | .642-1.314 | .640 |
| Avg RBP | .124 | 1.132 | 1.092-1.173 | .000* |
| **denotes statistical significance. OR, Odds Ratio; TST, Total Sleep Time; RBP, Resting Blood Pressure* | | | | |

Based on both the chi-square and logistic regression statistical approaches, this additional analysis found no association between $TST_{continuous}$, and an $EBPR_{Absolute}$ in the cohort of females aged 55 years and older.

3.4.2 $TST_{continuous}$ and Relative Blood Pressure Category

Using the same approach used in section 3.4.1, in this additional analysis I used TST as a continuous variable ($TST_{continuous}$). The mean TST for this cohort was 7.20 ± 0.92 hrs/night. The cohort was divided into two groups based on relative blood pressure category (1) $typical_{relative}$ blood pressure response to three minutes of moderate physical activity; and (2) $EBPR_{relative}$ to three minutes of moderate physical activity.

The method used to assess the association between $TST_{continuous}$ and an $EBPR_{Absolute}$ was a univariate logistic regression analysis (Table 12). In this model, the univariate logistic regression model did not detect statistically significant odds ratio for $TST_{continuous}$.

**Table 12:** Logistic Regression Models with Relative Blood Pressure Response Category and $TST_{continuous}$

| Outcome | Relative Blood Pressure Response | | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate Logistic Regression** | | | | |
| **$TST_{continuous}$** | -.350 | .705 | .461-1.077 | .106 |
| **denotes statistical significance. OR, Odds Ratio; TST, Total Sleep Time* | | | | |

Based on both the chi-square and logistic regression statistical approaches, this additional analysis found no association between $TST_{continuous}$, and an $EBPR_{relative}$ in the cohort of females aged 55 years and older.

3.5.1 Sleep $Quality_{SE}$ (Poor and Adequate Sleep Quality) Absolute and Relative Blood Pressure Category

In order to test hypothesis 5 and 6, I divided the cohort into two groups; namely (1) poor sleep quality of a SE <85%; and (2) adequate sleep quality ≥85%. Due to the COVID-19 pandemic, I was unable to recruit the 400 participants that I had originally planned to include in the analysis; rather, a cohort of 206 participants was analyzed. The mean sleep efficiency value was 91% (95% CI ± 3.49), well above the sleep efficiency cut-off value. Based on previous research-based cut-off values for SE, the prevalence of participants with poor sleep quality in the cohort was 4.9%; whereas, 95.1% of the cohort were classified as adequate sleep quality. Statistical testing was underpowered for hypothesis 5 and 6. As a result, they were not examined in my thesis. Hypotheses 5 and 6 will be examined at a future time using the full 1000 participants from the overall WARM Hearts trial after its completion.

### 3.6.1 $SE_{continuous}$ and Absolute Blood Pressure Category

Analyses that were identified after the writing of my thesis proposal were developed and will be addressed in the following section. In the first analysis, I used SE as a continuous variable ($SE_{continuous}$). The mean sleep efficiency value was 91% ± 3.49. The cohort was also divided into two groups based on absolute blood pressure category (1) $Typical_{Absolute}$ blood pressure response to three minutes of moderate physical activity; and (2) $EBPR_{Absolute}$ to three minutes of moderate physical activity.

The method used to assess the association between $SE_{continuous}$ and an $EBPR_{Absolute}$ was a logistic regression analysis (Table 13). The univariate logistic regression models did not detect statistically significant odds ratio for unadjusted $SE_{continuous}$. A multivariate logistic regression was then used to control for Avg RBP; however, it did not detect a statistically significant odds ratio for $SE_{continuous}$. However, Avg RBP was statistically significant in the multivariate model where presenting with an having a higher RBP prior to the 3-minutes of moderate physical activity increased the odds of presenting with an $EBPR_{Absolute}$ by 1.133 (CI±1.093-1.175).

**Table 13:** Logistic Regression Models with Absolute Blood Pressure Response Category and $SE_{continuous}$

| Outcome | Absolute Blood Pressure Response | | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate** | | | | |
| $SE_{continuous}$ | .019 | 1.019 | .938-1.108 | .657 |
| **Multivariate** | | | | |
| $SE_{continuous}$ | .054 | 1.055 | .953-1.168 | .299 |
| Avg RBP | .125 | 1.133 | 1.093-1.175 | .000* |
| **denotes statistical significance. OR, Odds Ratio. SE, Sleep Efficiency; RBP, Resting Blood Pressure* | | | | |

Based on the logistic regression statistical approaches, this additional analysis found no association between $SE_{continuous}$, and an $EBPR_{Absolute}$ in the cohort of females aged 55 years and older. When Avg RBP was controlled for in the logistic regression model, there was also no association between the Sleep $duration_{TST}$ and the $EBPR_{Absolute}$ in a cohort of females 55 years or older

3.6.2 $SE_{continuous}$ and Relative Blood Pressure Category

Using the same approach used in section 3.6.1, in this additional analysis I used SE as a continuous variable ($SE_{continuous}$). The mean sleep efficiency value was 91% ± 3.49. The cohort was also divided into two groups based on relative blood pressure category (1) $typical_{relative}$ blood pressure response to three minutes of moderate physical activity; and (2) $EBPR_{relative}$ to three minutes of moderate physical activity.

The method used to assess the association between $SE_{continuous}$ and an $EBPR_{relative}$ was a logistic regression analysis (Table 14). The univariate logistic regression models did not detect statistically significant odds ratio for unadjusted $SE_{continuous}$.

**Table 14:** Logistic Regression Models with Relative Blood Pressure Response Category and $SE_{continuous}$

| Outcome | | Relative Blood Pressure Response | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate** | | | | |
| $SE_{continuous}$ | .022 | 1.022 | .910-1.148 | .715 |
| **denotes statistical significance. OR, Odds Ratio. SE, Sleep Efficiency* | | | | |

Based on the logistic regression statistical approaches, this additional analysis found no association between $SE_{continuous}$ and an $EBPR_{relative}$ in the cohort of females aged 55 years and older.

3.7.1 Sleep Quality$_{PSQI}$ and Absolute Blood Pressure Category

Previous research has utilized a PSQI score of ≥5 as an indication that participants had poor sleep quality. Therefore, in order to test hypothesis 7, I divided the cohort into two groups; namely (1) poor sleep quality of a PSQI score ≥5 and (2) adequate sleep quality defined by a PSQI score <5. Using this metric, 57.3% (118 of the 206 participants in the cohort) were classified as having poor sleep quality$_{PSQI}$ and 88 individuals were classified as having adequate sleep quality$_{PSQI}$.

To further categorize the 188 participants who had poor sleep quality$_{PSQI}$, it was determined that 54 were classified as short sleepers$_{TST}$, 62 were classified as normal sleepers$_{TST}$, and 2 individuals were classified as long sleepers$_{TST}$ based on the PSQI total score. Of the 88

individuals who had proper sleep quality$_{PSQI}$, it was further determined that 30 participants were classified as short sleepers$_{TST}$, 56 were classified as normal sleepers$_{TST}$ and 2 participants were scored as long sleepers$_{TST}$.

To test hypothesis 7, I incorporated the groups (1) poor sleep quality$_{PSQI}$ of a PSQI score ≥5 and (2) adequate sleep quality$_{PSQI}$ <5. T-tests were used to examine differences in mean estimates of age, BMI, heart rate post moderate exercise, menopause onset, resting systolic blood pressure, post-secondary education, living arrangements, smoking status, HDL, LDL and total cholesterol, and FRS 10-year risk score. No significant differences between age, BMI, heart rate post-moderate exercise, menopause onset, resting systolic blood pressure, post-secondary education, living arrangements, smoking status, HDL, LDL and total cholesterol, or FRS 10-year risk score were identified. Table 15 describes the demographic information for the adequate sleep quality$_{PSQI}$ and poor sleep quality$_{PSQI}$.

**Table 15.** Participant Characteristics for PSQI Score

| | PSQI Score | | |
|---|---|---|---|
| Participant Characteristics | Adequate Sleep Quality$_{PSQI}$ | Poor Sleep Quality$_{PSQI}$ | p value |
| N (%) | 88 (42.37) | 118 (57.3%) | |
| Age, years | 64 ± 6.5 | 64 ± 5.8 | .474 |
| BMI, kg/m$^2$ | 25.4 ± 4.6 | 26.4 ± 5.3 | .156 |
| Heart rate post-moderate physical activity, bpm | 72 ± 14.7 | 74.6 ± 13.3 | .179 |
| Menopause onset, years | 50 ± 5.2 | 50.5 ± 5.4 | .556 |
| Resting systolic blood pressure, mmHg | 118 ± 12.7 | 120.2 ± 13.7 | .242 |
| Post-secondary education, n (%) | 83 (94.3%) | 107 (90.7%) | .438 |
| Living arrangement (alone), n (%) | 12 (13.6%) | 22 (18.6%) | .341 |
| Ex/current smoker, n (%) | 39 (44.3%) | 61 (51.7%) | .297 |
| HDL cholesterol | 1.77 ± 0.45 | 1.68 ± 0.41 | .117 |
| LDL cholesterol | 3.42 ± 0.90 | 3.55 ± 0.91 | .312 |
| Total cholesterol | 5.18 ± 0.92 | 5.28 ± 0.88 | .429 |
| FRS 10-year risk | 6.16 ± 3.65 | 6.99 ± 4.43 | .143 |
| *Continuous variables expressed as Mean ± standard deviation. Categorical variables expressed as frequency (percentage).* | | | |

The cohort was also divided into two groups based on absolute blood pressure category (1) Typical$_{Absolute}$ blood pressure response to three minutes of moderate physical activity; and (2) EBPR$_{Absolute}$ to three minutes of moderate physical activity. Of the full cohort of 206 participants, 134 (65%) participants had a typical$_{absolute}$ blood pressure response, where 72 (35%) participants had an EBPR$_{Absolute}$.

Four groups were created based on the two variables of sleep quality$_{PSQI}$ and absolute blood pressure response. The four groups created were (1) Poor sleep quality$_{PSQI}$ with a typical$_{absolute}$ blood pressure response; (2) Adequate sleep quality$_{PSQI}$ with a typical$_{absolute}$ blood pressure

response; (3) Poor sleep quality$_{PSQI}$ with an EBPR$_{Absolute}$; and (4) Adequate sleep quality$_{PSQI}$ with an EBPR$_{Absolute}$. For the four groups created (Table 16), the demographic continuous variable data was explored by a 2-ANOVA. There was a significant difference for the main effect between typical$_{absolute}$ and EBPR$_{relative}$ blood pressure response for age (p=.001), heart rate post moderate exercise (p=≤.001), BMI (p=≤.001) and average resting systolic blood pressure (p=≤.001). The EBPR$_{Absolute}$ blood pressure category group was older and had a higher BMI compared to the typical$_{absolute}$ blood pressure category.

The demographic categorical variable data, such as PS education, tobacco use and living arrangements was explored by a chi-square (Table 16). No differences were identified for PS education, living arrangements and tobacco use.

**Table 16:** Participant Characteristics for CVD Risk (Absolute) and Sleep Quality Groups

| | Typical$_{absolute}$ blood pressure response & Poor sleep quality$_{PSQI}$ | Typical$_{absolute}$ blood pressure response & Adequate sleep quality$_{PSQI}$ | EBPR$_{Absolute}$ & Poor sleep quality$_{PSQI}$ | EBPR$_{Absolute}$ & Adequate sleep quality$_{PSQI}$ | Sleep quality$_{PSQI}$ score P value | BP response P value | Interaction P value | Chi-square P value |
|---|---|---|---|---|---|---|---|---|
| N (%) | 75 (36.4) | 59 (28.6%) | 43 (20.9) | 29 (14.1) | | | | |
| Age, years | 68 ± 7 | 66 ± 6 | 62 ± 5 | 64 ± 6 | .419 | .001* | .980 | |
| HR Post PA, bpm | 76 ± 15 | 78 ± 12 | 74 ± 15 | 72 ± 14 | .516 | ≤.001* | .081 | |
| PS education, n (%) | 68 (91%) | 56 (95%) | 39 (91%) | 27 (93%) | | | | .859 |
| Living arrangement (Alone), n (%) | 12 (16%) | 8 (14%) | 10 (23%) | 4 (14%) | | | | .580 |
| Tobacco use (ex/current), n (%) | 49 (65%) | 36 (61%) | 12 (28%) | 3 (10%) | | | | .561 |
| BMI, kg/m$^2$ | 28.6 ± 6.0 | 28.5 ± 7.4 | 25.7 ± 4.4 | 25.5 ± 4.8 | .126 | ≤.001* | .373 | |
| Menopause onset, years | 51 ± 4 | 50 ± 5 | 51 ± 4 | 50 ± 6 | .341 | .980 | .178 | |
| Avg RBP, mmHg | 122 ± 10 | 124 ± 18 | 118 ± 13 | 119 ± 13 | .438 | ≤.001* | .457 | |

**denotes statistical significance. Abbreviation: HR, Heart Rate; PA, Physical Activity; PS, Post-secondary; BMI, Body Mass Index; Avg, Average; RBP, Resting Blood Pressure. Sample size 206.*

The chi-square test did not identify significant differences between any of the four groups. Summary information for the chi-square analysis is present in Table 17.

**Table 17.** Frequency Distribution of Absolute Blood Pressure Response and Sleep Quality$_{PSQI}$

| | Typical$_{absolute}$ blood pressure response | EBPR$_{Absolute}$ | P Value[a] |
|---|---|---|---|
| **PSQI score** | | | |
| >5 | 29 | 43 | .604 |
| <5 | 59 | 75 | |
| *[a]Chi-square P values comparing the distribution between typical absolute blood pressure response and exaggerated absolute blood pressure response. Sample size (n=206)* | | | |

The second method used to assess the association between sleep quality$_{PSQI}$ and an EBPR$_{Absolute}$ was a logistic regression analysis (Table 18). The univariate logistic regression models did not detect statistically significant odds ratio for unadjusted Sleep quality$_{PSQI}$. For the multivariate model, when controlling for Avg RBP, Sleep quality$_{PSQI}$ was also not statistically significant. However, Avg RBP was statistically significant in the multivariate model where presenting with an having a higher RBP prior to the 3-minutes of moderate physical activity increased the odds of presenting with an EBPR$_{Absolute}$ by 1.132 (CI ±1.092-1.174).

**Table 18:** Logistic Regression Models with Absolute Blood Pressure Response Category and Sleep Quality$_{PSQI}$

| Outcome | | Absolute Blood Pressure Response | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate** | | | | |
| Sleep quality$_{PSQI}$ | -.154 | .857 | .479-1.533 | .604 |
| **Multivariate** | | | | |
| Sleep quality$_{PSQI}$ | .079 | 1.082 | .531-2.208 | .828 |
| RBP | .124 | 1.132 | 1.092-1.174 | .000* |
| **denotes statistical significance. OR, Odds Ratio; PSQI, Pittsburgh Sleep Quality Index; RBP, Resting Blood Pressure* | | | | |

Hypothesis 7 was rejected, as both the chi-square and logistic regression statistical approaches found no association between sleep quality$_{PSQI}$ and an EBPR$_{Absolute}$ in the cohort of females aged 55 years and older. When Avg RBP was controlled for in the logistic regression model, there was also no association between the sleep quality$_{PSQI}$ and the EBPR$_{Absolute}$ in a cohort of females 55 years or older.

3.7.2 Sleep Quality$_{PSQI}$ and Relative Blood Pressure Category

Using the same approach described in section 3.7.1 for hypothesis 7, in order to test hypothesis 8, I divided the cohort into two groups; namely (1) poor sleep quality$_{PSQI}$ of a PSQI score $\geq$5 and (2) adequate sleep quality$_{PSQI}$ <5. Table 18 previously describes the demographic information for the adequate sleep quality$_{PSQI}$ and poor sleep quality $_{PSQI}$.

The cohort was also divided into two groups based on relative blood pressure response category (1) typical$_{relative}$ blood pressure response to three minutes of moderate physical activity;

and (2) $EBPR_{relative}$ to three minutes of moderate physical activity. Of the 206 participants, 177 (85.9%) had a $typical_{relative}$ blood pressure response, where 29 participants (14.1%) had an $EBPR_{relative}$.

Two methods were used to assess the association between sleep $quality_{PSQI}$ and an $EBPR_{relative}$. The first method was a chi-square analysis, where four groups were created. For the four groups created in the chi-square analysis, the demographic continuous variable data was explored by an ANOVA and a chi-square analysis was used to examine the demographic categorical variable data (Table 19) such as PS education, tobacco use and living arrangements. The four groups created were (1) Poor sleep $quality_{PSQI}$ with a $typical_{relative}$ blood pressure response; (2) Adequate sleep $quality_{PSQI}$ with a $typical_{relative}$ blood pressure response; (3) Poor sleep $quality_{PSQI}$ with a $EBPR_{relative}$; and (4) Adequate sleep $quality_{PSQI}$ with an $EBPR_{relative}$.

The 2-way ANOVA was used to determine significant main effects of sleep $quality_{PSQI}$ and $EBPR_{relative}$ and the interaction effects among the 4 groups. There was a significant difference for the main effect between $typical_{relative}$ and $EBPR_{relative}$ for age ($p=\leq.001$), and BMI ($p=.035$), where the $EBPR_{relative}$ group were older and had a higher BMI compared to the $typical_{relative}$ group. There was also a significant difference for the main effect between poor and adequate sleep quality ($p=.0.45$) for age, where the poor sleep $quality_{PSQI}$ group were older than the adequate sleep $quality_{PSQI}$ group. The chi-square that was used to compare the characteristics for the 4 groups for categorical data found no differences were identified for PS education, living arrangements and tobacco use.

**Table 19:** Participant Characteristics for CVD Risk (Relative) and Sleep Quality$_{PSQI}$ Groups

| | Typical$_{relative}$ blood pressure response & Poor sleep quality$_{PSQI}$ | Typical$_{relative}$ blood pressure response & Adequate sleep quality$_{PSQI}$ | EBPR$_{relative}$ & Poor sleep quality$_{PSQI}$ | EBPR$_{relative}$ & Adequate sleep quality$_{PSQI}$ | Sleep quality$_{PSQI}$ score P value | BP response P value | Interaction P value | Chi-square P value |
|---|---|---|---|---|---|---|---|---|
| N (%) | 96 | 81 | 22 | 7 | | | | |
| Age | 63 ± 6 | 64 ± 6 | 66 ± 6 | 71 ± 9 | .045* | ≤.001* | .115 | |
| HR Post PA | 74 ± 14 | 71 ± 14 | 76 ± 12 | 82 ± 12 | .593 | .051 | .116 | |
| PS education | 88 (92%) | 77 (95%) | 19 (86%) | 6 (86 %) | | | | .480 |
| Living arrangement (Alone) | 16 (17%) | 11 (14%) | 6 (27%) | 1 (14%) | | | | .497 |
| Tobacco use (ex/current) | 49 (51%) | 36 (44%) | 12 (55%) | 3 (43%) | | | | .755 |
| BMI | 25.8 ± 4.5 | 25.3 ± 4.7 | 29.1 ± 7.3 | 26.7 ± 2.1 | .195 | .035* | .385 | |
| Menopause onset | 51 ± 6 | 50 ± 5 | 50 ± 4 | 48 ± 8 | .230 | .297 | .317 | |
| Avg RBP | 120 ± 14 | 118 ± 13 | 123 ± 14 | 124 ± 13 | .870 | .125 | .594 | |

**denotes statistical significance. Abbreviation: HR, Heart Rate; PA, Physical Activity; PS, Post-secondary; BMI, Body Mass Index; Avg, Average; RBP, Resting Blood Pressure. Sample size 206.*

The chi-square test did identify significant differences between the four groups (p=.029). Summary information for the chi-square analysis is present in Table 25.

**Table 20.** Frequency Distributions of Relative Blood Pressure and Sleep Quality$_{PSQI}$

| | Typical$_{relative}$ blood pressure response | EBPR$_{relative}$ | P Value[a] |
|---|---|---|---|
| **PSQI score** | | | |
| >5 | 96 | 22 | **.029*** |
| <5 | 81 | 7 | |

*Abbreviation: SE, standard error. [a]Chi-square P values comparing the distribution between typical relative blood pressure response and exaggerated relative blood pressure response.*

The second method used to assess the association between sleep quality$_{PSQI}$ and an EBPR$_{relative}$ was a logistic regression analysis (Table 21). The univariate logistic regression models did detect statistically significant odds ratio for unadjusted Sleep quality$_{PSQI}$, where

having a higher Sleep quality$_{PSQI}$ score decreased your odds of having an EBPR$_{relative}$ by 0.337 (95% CI ± 0.153-0.93).

**Table 21:** Logistic Regression Model with Relative Blood Pressure Response Category and Sleep Quality$_{PSQI}$

| Outcome | Relative Blood Pressure Response | | | |
|---|---|---|---|---|
| | *B* | OR | 95% CI | P-Value |
| **Univariate** | | | | |
| Sleep quality$_{PSQI}$ | .975 | .377 | .153-.928 | .034* |
| **denotes statistical significance. OR, Odds Ratio; PSQI, Pittsburgh Sleep Quality Index* | | | | |

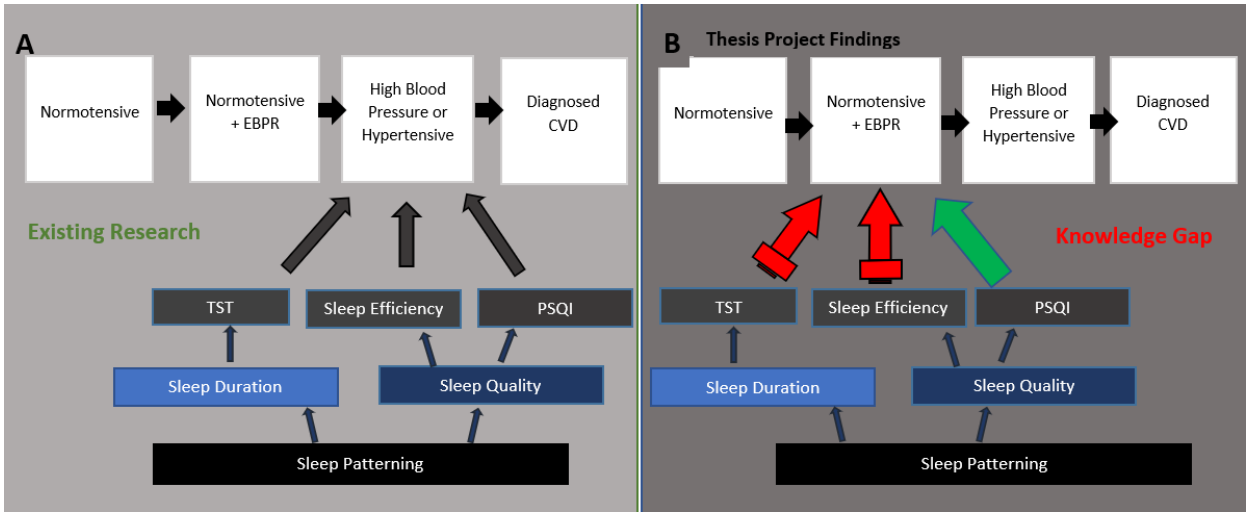
Hypothesis 8 was accepted, as both the chi-square and logistic regression statistical approaches found an association between sleep quality$_{PSQI}$ score and an EBPR$_{relative}$ in the cohort of females aged 55 years and older.

# Chapter 4: Discussion

## 4.1 Sleep Patterning and EBPR Category Summary

Resting blood pressure values have previously been reported to be elevated in populations with poor sleep patterning. However, the potential association between EBPR to 3-minutes of moderate physical activity and sleep patterning remains unknown, with no previous research found that addresses this knowledge gap. Therefore, I have examined this relationship in an all-female cohort, 55 years of age or older. This issue is important to examine because it is essential to determine if sleep patterning effects CVD risk, which in this project is being measured through the presence of an EBPR. Other researchers have reported that EBPR may better detect the risk for future hypertension or CVD than does conventional resting blood pressure measurement[38,62]. If an association between sleep patterning and EBPR is present, then healthcare professional can provide interventions to alter poor sleeping patterns to reduce future risk for cardiovascular complications and adverse events in older aged females. Therefore, the primary objective of my thesis were to determine if sleep patterns associate with an EBPR to 3-minutes of moderate physical activity in a cohort of women 55 years of age and older. A summary of existing research and my thesis project findings summary is represented in Figure 4.

**Figure 4:** The Association Between Sleep Pattering and Blood Pressure Progression in Existing Research (Panel A) and My Thesis Research Project (Panel B)




Represented in Figure 4, Panel A is the common pathway observed for blood pressure progression in the existing literature. My research supports the existing research, as demonstrated in Figure 4 (Panel B). This figure starts with a normotensive response in individuals and progresses to individuals who are normotensive but demonstrate an EBPR to moderate physical activity. The EBPR is situated before the hypertensive response because individuals may be normotensive, but when the system is presented with an external stressor, such as 3-minutes of moderate physical activity, the body is unable to buffer the stressor, leading to an increase in sympathetic nervous system and blood pressure. Progressing forward in the model, individuals who are unaware of this EBPR may progress to high blood pressure or the diagnosis of hypertension, progressively leading to other diagnoses of CVD.

Figure 4 also describes how sleep patterning is categorized within the existing research as well as in my research project which replicates this approach using EBPR rather than determining the relationship with RBP. Sleep patterning has been assessed using both sleep duration and sleep quality. Specifically, sleep duration in my research project was assessed using

TST, assessed by accelerometry and further categorized into short, normal, and long sleep duration. Additionally, sleep quality was assessed using both an objective and subjective method. For objective sleep quality, the most typically used method in current research, beside the gold standard PSG, is using accelerometry based SE which was categorized as ≥85% (adequate sleep quality) and <85% (poor sleep quality). The subjective method used for sleep quality was the PSQI global score which was categorized as a score <5 (adequate sleep quality and ≥5 (poor sleep quality).

Previous research has demonstrated the association between sleep patterning and diagnosed hypertension based on resting blood pressure or CVD[97,98,98–101]. Significant associations have been found in existing research, where the prevalence of hypertension is associated with sleep duration, assessed by TST, objective SE and subjective PSQI score[79,98,102–105],(Figure 4, Panel A), which is demonstrated using gray arrows. Current research excludes the association between sleep patterning and an EBPR, which is represented with green and red arrows in Figure 4, Panel B, which indicates the knowledge gap in research. My research addressed the knowledge gap to see if sleep patterning is associated with an EBPR, which may earlier detect CVD risk in females over the age of 55 years. The overall findings are demonstrated in Figure 4, Panel B for my research project, where no association was found in regards to the association between objectively measured TST as a categorical variable (short vs normal sleep duration$_{TST}$) and a continuous$_{TST}$ variable or SE as a continuous variable and EBPR categories demonstrated by a red arrow with a closed end. However, there was an association found between PSQI and a relative EBPR which is demonstrated by a green arrow. Further information about the findings of my research project is described in section 4.2, 4.3, and 4.4.

4.2 Sleep Duration$_{TST}$ and blood pressure response category groups

There is a paucity of information about the association between sleep duration$_{TST}$ and EBPR category groups. An EBPR to moderate physical activity may be a more sensitive approach to detect CVD risk and autonomic dysfunction then resting blood pressure. My research addressed this knowledge gap looking at the difference between sleep patterning, more specifically sleep duration$_{TST}$ and an EBPR category groups. The mean total sleep time in hours was 7.20 hrs, which falls in the previously described normal sleep duration cut-off[23]. The overall trend of sleep duration was skewed towards what is typically described as short sleep duration, which varies compared to previous studies assessing sleep duration, which typically follows a normal distribution of short, normal and long sleep duration. Based on the t-test, participants who had normal sleep duration were older, compared to participants who had short sleep duration.

My thesis findings do not support previous studies,[48,53,79,106] which report that people with short sleep duration have a greater risk for hypertension. These difference may have been caused by using RBP to assess this risk of hypertension, where this thesis used EBPR to assess CVD risk. For example, the 10-year CVD risk was low in the cohort based on the FRS. This may have been due to the sampling method used to recruit participants, where the overall WARM Hearts study used a convenience sampling method. This may have led to the recruitment of participants who are health consumers and more health conscientious.

Finding no associations between sleep duration$_{TST}$ and EBPR category, we can not assume that sleep duration$_{TST}$ and EBPR are associated and that using an EBPR will better clinically assess CVD risk. Even so, it is important to acknowledge that with a larger sample size, the association between sleep duration$_{TST}$ and EBPR may be present. In a study by Gottlieb et al. which assessed the association between subjective sleep duration and hypertension in a

population of 5910 participants (2813 men, 3097 women). 1749 participants (29.6%) were classified as having short sleep duration of < 7 hours per night. It was found that participants who had short sleep duration were associated with having hypertension. Although this study uses subjective sleep duration methods, it demonstrates the importance of using large sample sizes and significantly high-powered groups to find associations that may be present.

Although no current research has addressed the association between sleep duration$_{TST}$ and an EBPR, previous research has looked at the association between sleep duration and hypertension, most typically measured through resting blood pressure. Sleep duration is strongly associated with cardiovascular disease risk, and more specifically blood pressure regulation. Two cross-sectional studies found short sleep duration to be associated with hypertension prevalence only in female subjects[103,106]. However, Bansil et al. demonstrated that in a cohort of 10,308 participants, there was no significant association among adults with short sleep duration (<7hrs/night) and hypertension[107]. These contraindicatory findings may be due to inconsistencies in sleep duration definition and the methods used to assess sleep duration

4.3 Sleep Efficiency$_{continuous}$ and blood pressure response category groups

My research addressed this knowledge gap looking at the difference between sleep patterning, more specifically sleep efficiency assessed by accelerometry and an EBPR category groups. My research generated data that differed from literature previously published. For example, in previous research, the sleep efficiency score assessed by accelerometers has been captured using a categorical approach of ≥85% or <85%. Due to the fact that the overall sample size of this cohort was limited due to the COVID-19 pandemic, I was unable to include this approach of using a sleep efficiency as a categorical variable. I made the decision to move forward with analyzing SE as a continuous variable, which is less often used in current research.

My work reports that there was no significant association between sleep efficiency$_{continuous}$ and the blood pressure response group (absolute or relative). The mean sleep efficiency score of this cohort of females over the age of 55 years was 91.6% ± 3.49, which is well over the cut-off point of adequate sleep quality (≥85%). The high sleep efficiency score in this population may have been because the trend of sleep duration was skewed toward the short sleep duration cut-off. Future analysis, using the full WARM Hearts cohort (n=1000) will be better powered to assess the relationship between SE, using the categorical cut-off, and EBPR category groups.

Recent studies suggest that sleep quality, independent of sleep duration, may play an important role in blood pressure regulation[98,108,109]. The measurements of objective sleep quality has been positively associated with hypertension, such as lower sleep efficiency (being asleep for less than 85% of the time in bed). Additionally, contradictory findings have been found in relation to objective sleep efficiency measures and nocturnal systolic arterial pressure[108]. While some studies report a significant correlation between reduced sleep efficiency and a blunted nocturnal systolic arterial pressure [97,99], others report no association[78,100]. These contradictory findings may be due to differing methods of assessing sleep efficiency in these research studies. For example, Sherwood et al.[99] used actigraphy SE measurements to assess the association with blood pressure dipping, where Loredo et al.[100] used PSG to assess SE and the association with blood pressure dipping. Using PSG to assess SE may be a more sensitive approach, then actigraphy because it incorporates a wider range of measurements including the differentiation of REM and NREM. Additionally, Ross et al. demonstrated in twenty-three healthy young adults, that twenty-four-hour blood pressure was not different between sleep efficiency groups. However, Doyle et al. revealed that lower average sleep efficiency (<85%) was associated with higher average daytime systolic blood pressure,

measured by ambulatory blood pressure[101]

4.4 Sleep quality$_{PSQI}$ and blood pressure response category groups

To my knowledge, this is the first time that the PSQI score, based on literature cut-offs, has been assessed with the association of an EBPR category. In the ANOVA analysis with poor quality$_{PSQI}$ and EBPR$_{relative,}$ participants in the poor sleep qualityPSQI group were older compared to participants in the adequate sleep quality$_{PSQI}$. In the chi-square analysis, it was determined that there was a significant association in the sleep quality$_{PSQI}$ and the EBPR$_{relative}$ ($p=.029$). This finding shows that participants who had poor sleep quality$_{PSQI}$ are more likely to have an EBPR$_{relative}$ to 3-minutes of moderate physical activity. Additionally, it was also found in the logistic regression model that there was a significant association between sleep quality$_{PSQI}$ and EBPR$_{relative.}$ This analysis determined that having a lower sleep quality$_{PSQI}$ score, meaning adequate sleep quality, decreased your odds of having an EBPR$_{relative}$ by 0.337 or having a reduction of 63%. Sleep restrictions alter the autonomic balance and increases the sympathetic nervous system activity which may be because of poor sleep quality resulting in non-dipping blood pressure patterns. Individuals who are known as non-dippers, meaning having a reduction of blood pressure than 10% during sleep compared to their mean daytime blood pressure values have an increase in sympathetic nervous system activity during the day.

The PSQI is a popular and clinically accepted instrument of choice because of its high internal consistency ($a = 0.83$), and test-retest reliability ($r = .85$) [20] and moderate structural variability identifying patients with poor sleep quality in both clinical and nonclinical populations[98]. It differentiates poor from adequate sleep quality by measuring seven sleep components. In a meta-analysis which included 45 041 in total, eight of the studies which were included in this meta-analysis looking at subjective sleep quality and hypertension, poor sleep

quality was significantly associated with a greater likelihood of hypertension (OR, 1.48; 95% CI 1.13-1.95)[98].

## 4.5 Limitations

There are some limitations in the current study design. This research is a secondary analysis of the baseline data collected by the WARM Hearts trail. As such, the variables collected and analysed in this work were limited to the variables included in the WARM Hearts observational research trial. For example, the gold standard approach in research for assessing sleep patterning is polysomnography test, which was not included in the WARM Hearts study. It is important to acknowledge that the assessment tools used to assess sleep may not fully capture an individual's sleep patterning over a participant's full lifespan, as well as differentiating components of sleep such as REM and NREM sleep.

The WARM Hearts study used a convenience sample method for recruiting participants. This means of recruitment could create potential sample bias, where the population did not adequately represent the overall population of Manitoba. Females interested in the WARM Hearts study are more likely to be health consumers, leading them to be more aware of their overall lifestyle and health behaviours.

Additionally, due to the COVID-19 pandemic which started in March 2020, this research project had a smaller sample size of participants then originally planned. The original plan for this research project was to include 400 females over the age of 55 years, but due to the COVID-19 pandemic, only 206 females were included in analysis. The smaller sample size impacted the power to detect differences between groups for both the sleep efficiency and sleep duration$_{TST}$

parameters. In fact, less than 3% of the population were categorized as poor sleep quality based on literature cut-off values. Due to this, sleep efficiency was also examined as a continuous variable. Hypotheses 3 and 4 were not analysed because few long sleepers were identified (i.e.; Sleep duration$_{TST\ making}$ up less than 2% of the overall cohort) and the analyses would have been underpowered. The reduction in the overall sample size could have drastically affected the results of this study. Sleep quality$_{PSQI}$ score had a better distribution and was better powered for statistical testing based on the two groups of poor and adequate sleep quality compared with sleep duration$_{TST}$ and sleep quality$_{SE}$. It has also been shown that subjective sleep quality scores and objective measures of sleep quality through accelerometers often show a relatively modest or even non-existent relationship[110], which could explain an association found for PSQI score, but not sleep qualitySE.

Additionally, the measurements of sleep quality$_{PSQI}$ score and objective accelerometer assessments differ as sleep quality$_{PSQI}$ score is based on self-report questions about usual sleep patterns in the previous month, where accelerometer data of sleep duration$_{TST}$ and sleep quality$_{SE}$ was based off of a period of 7 days. Sleep qualityPSQI may be a better method to assess sleep quality because of the longer duration a person has to recall their sleep behaviours.

Another limitation of this study was that I did not control for variables in the statistical models that may have directly impacted the relationship of sleep patterning and EBPR. These variables include, but are not limited to, the diagnosis of sleep disorders, caffeine consumption, hypertensive medication use and smoking status. It was found in this cohort that 48.5% of the cohort were Ex or current smokers, which is higher than the national average of adult smoking prevalence in females of 14%[111]. With this, future studies should control for smoking status because it has been found in existing literature that smoking impacts both sleep patterning and

BP.

Future Directions

Future research to address the association between sleep patterning and EBPR categories should use the full WARM Hearts cohort (n=1000). Using a larger sample size may allow for the detection of change and association between groups. Also using a large sample size may allow us to look at long vs. normal sleep during and accelerometer SE as a categorical variable. Assessing sleep quality with the full WARM Hearts cohort should include the approach including categorical objective sleep efficiency score and sleep quality$_{PSQI}$ compared to EBPR response categories. It is important to consider that even though self-reported, subjective sleep quality scores are more often used to assess sleep quality in current research, using a subjective approach tends to lead to larger levels of variability in different populations, compared to objectively used measurements.

Future research may look at the association of sleep patterning and ambulatory blood pressure. Using ambulatory blood pressure over a 24-hour period may better detect blood pressure patterning. Another way to detect sleep patterning and autonomic dysfunction is through the assessment of heart rate variability. This approach has previously shown the balance between the sympathetic and parasympathetic nervous system.

Future research should use the gold standard approach, the PSG, and the association with and EBPR to moderate physical activity. Using the PSG may give a more accurate representation of sleep patterning and may be able to detect sleep disorders that accelerometers and PSQI score can not detect. Using PSG will allow to include controlling for the prevalence and diagnosed sleep disorders in analyses to see how models change when controlling for these factors

compared to univariate models.

If more research is done in the future to examine sleep patterning and EBPR or sleep patterning and autonomic dysfunction, the data may inform the development of new interventions, including an intervention that focuses on sleep behaviours. In fact, researchers will be the ones who create and test (research) the novel intervention. Example interventions may include sleep hygiene education programming, which may incorporate strategies to reduce screen time, caffeine consumption and other behavioural and health factors that may affect sleep. If those approaches prove to have efficacy in randomized controlled trials, then the approaches may be disseminated to health policy makers and implemented to improve primary risk prevention programming in the community.

## Conclusion

Sleep is essential for overall functioning and health status, including cardiovascular health. Furthermore, women are at an increased risk for developing future hypertension and CVD. In existing research, it has been identified that poor sleep patterning, including improper sleep duration and poor sleep quality is associated with hypertension prevalence and CVD risk. Identifying if poor sleep patterning places an individual at increased risk for CVD could assist with the design of interventions to modify and improve poor sleep patterning. My thesis demonstrated the association of EBPR and PSQI score based on the cohort of females aged 55 years and older. Such an approach of using EBPR will allow for the early detection of CVD risk, which may be affected by poor sleep patterning that can not be seen when measuring RBP. Additionally, this is an important contribution because sleep patterning may be a simple behavioural modification to help decrease overall CVD risk. My thesis data also identified that there was no significant association between EBPR categories and objective measures of sleep

duration$_{TST}$ and SE (assessed by accelerometry). The association of objective sleep patterning and EBPR categories may be better assessed with using a larger sample size, such as the full WARM Hearts cohort (n=1000). Additionally, there was an association found between sleep quality$_{PSQI}$ and an EBPR$_{relative}$, where participants with lower sleep quality$_{PSQI}$ score had lower odds of having an EBPR$_{relative}$ This finding highlights the need for future research, where the association between sleep patterning may be present in a larger population. By detecting an EBPR and determining if there is an association with sleep patterning, health care professionals may be able to recommend or prescribe lifestyle or clinical interventions to modify sleep behaviour to lessen CVD risk overall.

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## 2.5 Appendices

Appendix 1: The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines

Appendix 2: Sex and Gender Equity in Research (SAGER) guidelines

Appendix 3: Particpant consent form for WARM Hearts study

Appendix 4: Standardized Operating Procedures (SOP) for the download and analysis of accelerometer sleep data

Appendix 1: The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

| Item No | Recommendation | Page No |
|---|---|---|

| | | | |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 10-26 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 27-30 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 30 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 30, 31 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 31 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 32-37 |
| Bias | 9 | Describe any efforts to address potential sources of bias | |
| Study size | 10 | Explain how the study size was arrived at | |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 32-37 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 37,38 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | |
| | | (*c*) Explain how missing data were addressed | |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 35 |

| | | | |
|---|---|---|---|
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 44,45 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 46-54 |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 44-68 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | |
| | | (*b*) Report category boundaries when continuous variables were categorized | |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 69-75 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 76,77 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine

at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 2: Sex and Gender Equity in Research (SAGER) guidelines

| Research approaches ✓ | |
|---|---|
| ✓ | ✓ Are the concepts of gender and/or sex used in your research project? |
| | ✓ If yes, have you explicitly defined the concepts of gender and/or sex? Is it clear what aspects of gender and/or sex are being examined in your study? |
| | ✓ If no, do you consider this to be a significant limitation? Given existing knowledge in the relevant literature, are there plausible gender and/or sex factors that should have been considered? If you consider sex and/or gender to be highly relevant to your proposed research, the research design should reflect this |

| | |
|---|---|
| Research questions and hypotheses | |
| ✓ | ✓ Does your research question(s) or hypothesis/es make reference to gender and/or sex, or relevant groups or phenomena? (e.g., differences between males and females, differences among women, seeking to understand a gendered phenomenon such as masculinity) |
| Literature review | |
| ✓ | ✓ Does your literature review cite prior studies that support the existence (or lack) of significant differences between women and men, boys and girls, or males and females? |
| ✓ | ✓ Does your literature review point to the extent to which past research has taken gender or sex into account? |
| Research methods | |
| ✓ | ✓ Is your sample appropriate to capture gender and/or sex-based factors? |
| ✓ | ✓ Is it possible to collect data that are disaggregated by sex and/or gender? |
| ✓ | ✓ Are the inclusion and exclusion criteria well justified with respect to sex and/or gender? (Note: this pertains to human and animal subjects and biological systems that are not whole organisms) |
| ✓<br>✓ | ✓ Is the data collection method proposed in your study appropriate for investigation of sex and/or gender? |
| ✓ | ✓ Is your analytic approach appropriate and rigorous enough to capture gender and/or sex-based factors? |
| Ethics | |
| ✓ | ✓ Does your study design account for the relevant ethical issues that might have particular significance with respect to gender and/or sex? (e.g., inclusion of pregnant women in clinical trials) |
| *Source: Adapted from Canadian Institutes of Health Research* | |

* Researchers who are interested in the data regarding the SAGER guidelines can contact Dr. Todd Duhamel to request access to the data. The full cohort of 206 used for this analysis identified as women.

Appendix 3: Particpant consent form for WARM Hearts study

Research Participant Information and Consent Form

**Women's Advanced Risk Assessment in Manitoba (WARM) Hearts – Examining biomarkers of frailty and cardiovascular health in middle aged and older women**

**Principal Investigator:** Todd Duhamel, PhD

Faculty of Kinesiology and Recreation Management, University of Manitoba & Institute of Cardiovascular Sciences, St. Boniface General Hospital Research Centre, R4012 - 351 Tache Ave, Winnipeg, MB, Canada

R2H 2A6

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the research staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or (if applicable) your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the research staff to explain any words or information that you do not clearly understand. This study is funded by the St. Boniface Hospital Foundation.

**Purpose of Study:**

Efforts to prevent disease of the heart and blood vessels (i.e. the cardiovascular system) focus on the traditional risk factors, such as age, sex, cholesterol and blood pressure. This method is shown to predict heart attacks; however, it is likely the method could be improved by adding new measurement approaches.

The purpose of this research study is to establish a cardiovascular (CV) health screening program in Winnipeg and will test how well a new CV screening program works for detecting CV events over a 5-year period. A total of 1000 women will be recruited to participate in this study.

**Study procedures**

If you choose to participate in the study, you will be asked to attend two testing appointments; one at the Asper Clinical Research Institute and then one at the Active Living Centre at the University of Manitoba approximately one week later. Study appointment 1 will take approximately 2 hours and appointment 2 will take approximately 90 minutes.

***Study appointment 1***

During the first meeting, you will be asked to provide your Personal Health Information Number (PHIN), which is needed so we can collect information about how you utilize the health care system over the next 5-year period after screening. Your PHIN will be given a coded number so that your personal health information is not compromised. This method of coding PHINs is in accordance with the Personal Health Information Act (PHIA) of Manitoba and is a step taken to protect the privacy of your health information.

You will also be asked to complete a series of tests during your first appointment including:

1. A series of questionnaires to characterize demographic information and medical history;
2. Height and weight measurements
3. Body composition measurements;
4. Completion of a 6-minute walking test with heart rate assessment;
5. Functional fitness testing;

***Take-home assessments***

Between the first and second testing appointment, you will be asked to complete a series of questionnaires either on paper or via REDCap online survey. This series of questionnaires will characterize:

1. Physical activity level;
2. Diet;
3. Health risk behaviors and readiness to change;
4. General mood status,
5. Quality of life;

6. Frailty;
7. Ability to perform activities of daily living;
8. Typical sleep patterns;
9. Behaviour when receiving health information

Additionally, you will be asked to wear an accelerometer for the approximately weeklong period between appointments to capture objective physical activity measures and to collect a stool sample to characterize gut microbiota. At your first appointment, you will be provided with a kit and instructions for collecting a small stool sample at home before your second appointment approximately one week later.

***Study Appointment 2***

During the second appointment a blood sample will be collected (15 ml/1 tablespoon) to measure cholesterol, blood sugar, and other markers of cardiovascular disease. These additional markers will examine immune cell function and proteins found in your blood. The immune system works to protect the body against disease and infection. Cells involved in the immune system can be examined to see how well they are working and how many there are. Proteins are basic components found throughout your body that play important roles in a wide variety of body functions including building and repairing tissue. The remaining tests are non-invasive and include:

1. A non-invasive measure of arterial stiffness;
2. Resting blood pressure;
3. Blood pressure in response to 3 minutes of exercise;
4. A questionnaire to characterize symptoms of depression.

Blood and stool sampling collected as a part of this study will be kept in a lockable freezer on the 3rd floor of the Asper Clinical Research Institute. Your biological samples will not contain any personal information that could compromise confidentiality. Blood and stool samples will be stored for approximately 10 years and then destroyed. You will be asked to complete an additional consent form to retain leftover biological samples in a biobank which would provide scientists with access to the blood and stool samples to conduct future research.

Additional data for this project will be collected by linking your test data with your health information for a period of 5 years after the CV screening is completed. In order to monitor this information, we plan to utilize your PHIN and the Population Health Research Data Repository at the Manitoba Centre for Health Policy to collect information about how you interact with the health care system for a period of 5 years after the CV screening is completed. Research staff will review information in order to evaluate the effectiveness of the project for determining how

well our cardiovascular health screening program assesses cardiovascular health for a period of 5 years after the CV screening is completed. Your health records may include information such as:

1. health service use;
2. information relating to cardiovascular health;
3. other health problems; and
4. demographic information including age and household income;

All data will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Any information that may reveal personal identifiers (such as name, address or telephone numbers) will be removed prior to data analysis in order to protect patient anonymity and confidentiality.

Risks

With respect to safety, the risks associated with blood draws include pain, bruising, and a small risk of infection. There is a very minor risk associated with performing the physical activity testing. Other than blood sample collections all other tests to be completed are non-invasive and low-risk.

There is a potential risk of unintended disclosure of confidential information to parties outside the research context that might affect your ability to get insurance or a job. However, these risks are quite remote since appropriate confidentiality measures will be taken to protect any information about your health that is revealed by your biological samples.

One of the surveys that you will be asked to complete will assess signs of depression. If you are deemed to be at risk for potential depressive behavior, research staff are instructed to get a health care provider at the St. Boniface Hospital to speak with the participant to assess their risk. If a primary health care provider is not available, research staff will escort the participant to the Emergency Room at the St. Boniface General Hospital.

You are free to withdraw from participation in the study, withdraw your research data from the study or withdraw your biological samples from the study at any time upon request. Withdrawal from the research study will not alter the standard of care you receive. Your participation in the study may also be discontinued upon the advice of the medical staff for your safety.

In the case of injury or illness resulting from this study, necessary medical treatment will be available at no additional cost to you. If the research team becomes aware of a condition that may affect your health, the research team will share this information with medical staff at the St Boniface Hospital in order to enable them to provide you with appropriate care. You are not waiving any of your legal rights by signing this consent form, nor releasing the investigator(s) from their legal and professional responsibilities.

Benefits

A benefit to participating in this study is that you will gain specific and detailed information regarding your cardiovascular health. We will provide you with detailed information regarding your physical activity behaviours, physical fitness, and blood pressure response to moderate intensity exercise, which is not currently available to participants in the health care setting. Results collected as part of the WARM Hearts study are for research purposes only and are not diagnostic, but the information provided may help you make an informed decision about whether you would like to seek medical advice from a primary care provider. Although this information may help you to adopt a healthier lifestyle, your health status may or may not be influenced by your participation in the study. If your research results are indicative of high cardiovascular disease risk, you will be informed that you should speak to your primary healthcare provider to have diagnostic testing performed.

Information from this study could help create a new CV disease screening tool. That tool may someday help physicians and other health care providers to provide better care for their patients by preventing cardiovascular problems. This new information may be used to guide the development of future CV health initiatives.

Confidentiality

Information gathered in this research study may be published or presented in a program evaluation report to inform Manitoba Health and key stakeholders about the outcomes of the study. Medical records that contain your identity will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. The data collected from you during this study may be shared in an anonymized or de-identified form with academic journals for publication purposes or other researchers according to international guidelines. However, your name and other identifying information will not be used or revealed in the publications. The data may also be stored by the academic journal under an open access policy in which case it may be used by other researchers for further data analysis and research purposes. Before publishing/sharing any of the data, researchers will need to sign a data access and confidentiality agreement.

All research data related to you will bear only your assigned patient code. All records will be kept in a locked secure area and only those persons identified as Research Staff will have access to these records. Blood and stool samples will be coded with your unique Participant ID and will not contain any other information that could identify you in any way. If any of your medical/research records need to be copied, information that may reveal personal identifiers will be removed. Blood and stool samples will be kept in a lockable freezer and will be labelled with your participant ID number so they can be linked to other study documentation (e.g.

questionnaires, test procedure outcomes). Only Research Staff will have access to linkable information and that information will be kept confidential by law. The Research Electronic Data Capture (REDCap) system will also be used to support electronic data capture for participants willing to complete surveys online and for research data storage. The server for REDCap is stored within the Secure Research Environment of the Rady Faculty of Health Sciences.

No information revealing any personal information such as your name, address or telephone number will leave the Asper Clinical Research Institute/Active Living Centre nor will it be used for unauthorized purposes. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. The University of Manitoba Health Research Ethics Board and the St. Boniface General Hospital may review research-related records for quality assurance purposes. After the completion of the study, research data will be kept for a maximum of 10 years and then destroyed. This information will be protected as confidential in accordance with the Personal Health Information Act of Manitoba.

Feedback

Participants in the study will be provided an opportunity to request specific feedback about their individual results as well as the overall results of the study. If you would like to receive feedback, please provide your contact information on the "Feedback Request Form" at the end of this consent form package. Research staff will provide individual feedback upon request.

## Costs

All research-related procedures, which will be performed as part of this study, are provided at no cost to you.

Payment for participation

No compensation will be provided for participating in this study.

## Alternatives

Instead of being in this study, you may request educational material about cardiovascular disease.

Voluntary Participation/Withdrawal From the Study

Your decision to take part in this study is voluntary. You may refuse to participate or you may withdraw your data and biological samples from the study at any time by contacting the Duhamel Lab at (204) 480-1815 or *warmheartsresearch@gmail.com*. Your decision not to participate or to withdraw from the study will not affect your other medical care at this site. If medical staff determines that it is in your best interest to withdraw you from the study, the medical staff will inform the research team and will remove you from the study without your consent.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study.

Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact Dr. Todd Duhamel by phone at (204) 480-1815 or *warmheartsresearch@gmail.com*. For questions about your rights as a research participant, you may contact the University of Manitoba **Health** Research Ethics Board at (204) 789-3389.

A copy of this consent form will be given to you to keep for your records and reference.

**Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all questions.**

Statement of Consent

I have read this consent form. I have had the opportunity to discuss this research study with Dr. Todd Duhamel and/or his study staff. I have had my questions answered by them in language I understand. The risks and benefits have been explained to me. I believe that I have not been unduly influenced by any study team member to participate in the research study by any statement or implied statements. Any relationship (such as employee, student or family member) I may have with the study team has not affected my decision to participate. I understand that I will be given a copy of this consent form after signing it. I understand that my participation in this study is voluntary and that I may choose to withdraw at any time. I freely agree to participate in this research study.

I understand that any blood and stool samples collected will be kept in a lockable freezer for a 10-year period and will be labelled to only contain my participant ID to link to other study documentation (e.g. questionnaires, test procedure outcomes). I understand that information regarding my personal identity will be kept confidential, but that confidentiality is not guaranteed. I authorize the inspection of my research study documents by the University of Manitoba Health Research Ethics Board, the St. Boniface General Hospital in the event that an audit is conducted. By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

Participant signature:_____ Date:_____

Participant printed name: _____ Time:_____ AM/PM

***Research Staff***

*I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent*

*Printed Name:*_____ *Date:* _____

*Signature:* _____ *Time:*_____*AM/PM*

*Role in the study:* _____ *Relationship to study participant:* _____

Feedback Request Form

Do you agree to be contacted for a future research study?

Yes ☐ No ☐

I would like to receive:

_____ a specific feedback report detailing my individual results and a summary report of the overall study findings.

Participant signature: _____ Date: _____

Participant printed name: _____Time:_____AM/PM

**Please send me a copy of these reports by:**

_____ mail to the following mailing address:

_____

Appendix 4: Standardized Operating Procedures (SOP) for the download and analysis of accelerometer sleep data

Author: Alexandra Rose

# Appendix 4: Standardized Operating Procedures (SOP) for the download and analysis of accelerometer sleep data

# Equipment and Information

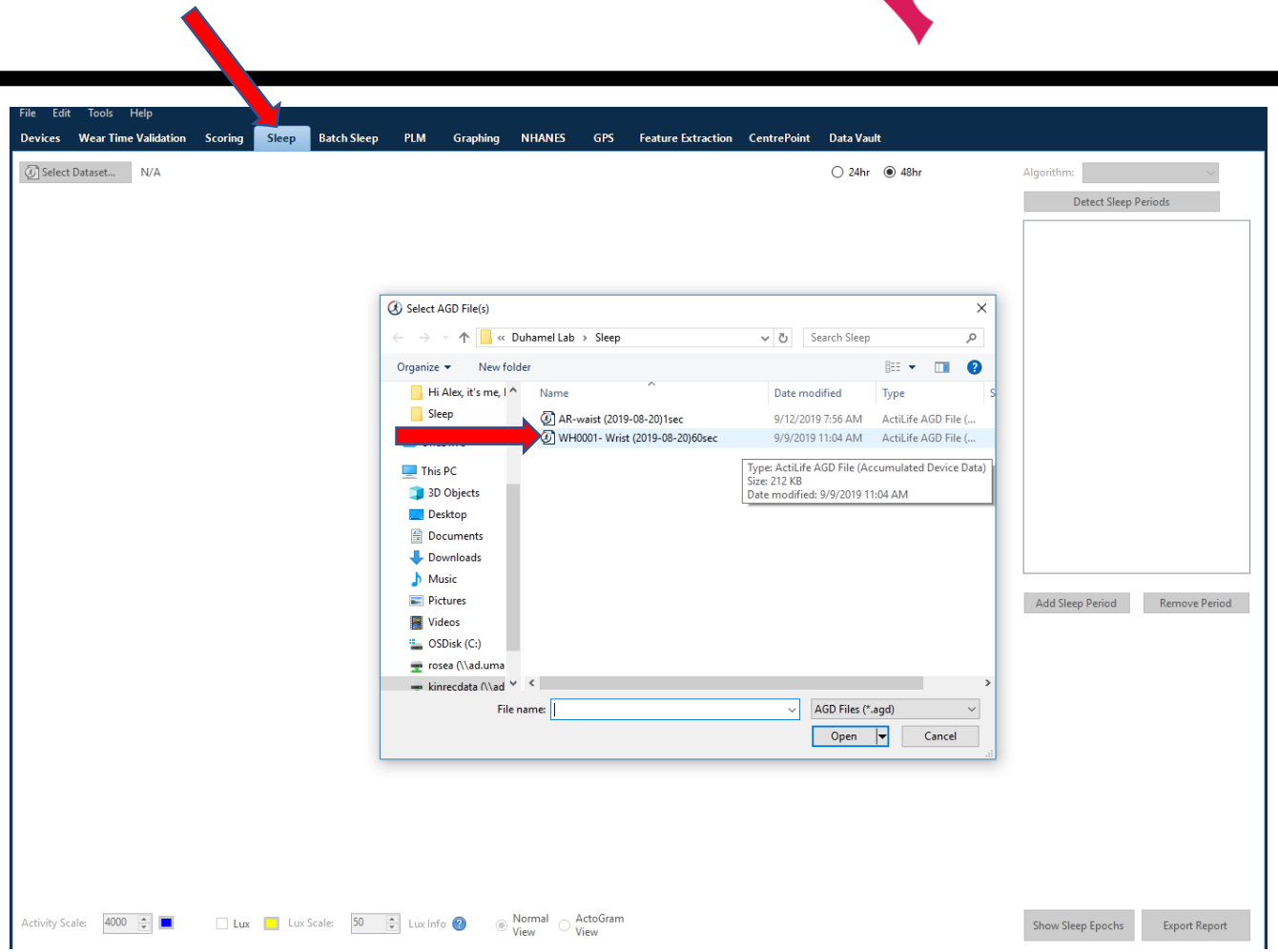
- Participant Sleep Log
- ActiLife Software
- Participants Actigraphy accelerometer (if not downloaded yet)

# Open Actilife

- **Ensure participants Sleep Log is in front of you before going through this SOP**
- Open Actilife software
- Participants accelerometer data should already be downloaded

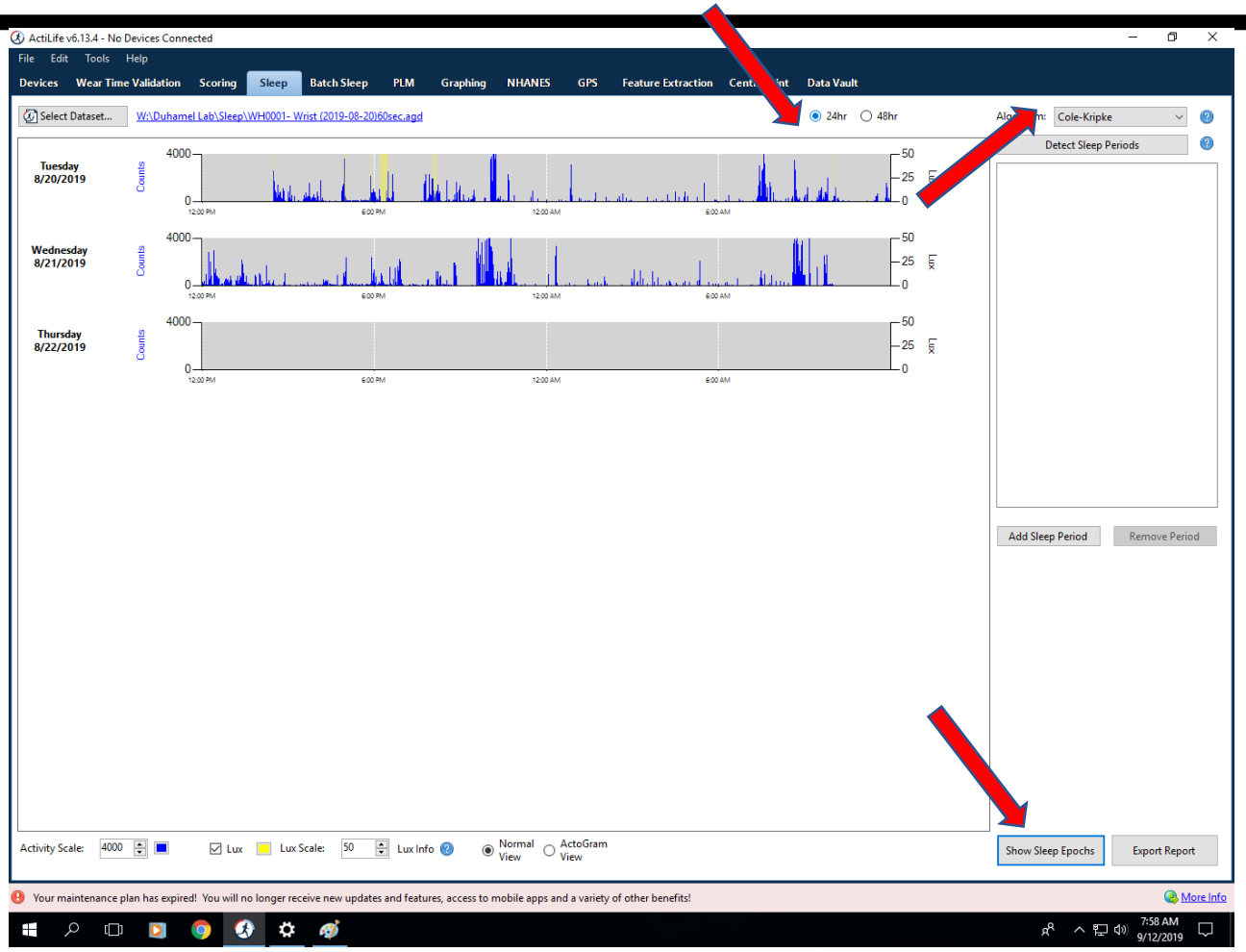
# Sleep

- Click “Sleep” tab at top of screen
- Click “Select Dataset”
- Under ABD File click “kinrecdata W:drive”, “Duhamel Lab”, “Sleep”
- Click on file labelled “participant ID-Wrist (Date) 60sec”
  - WH0001 – Wrist – 09/12/2019 – 60sec



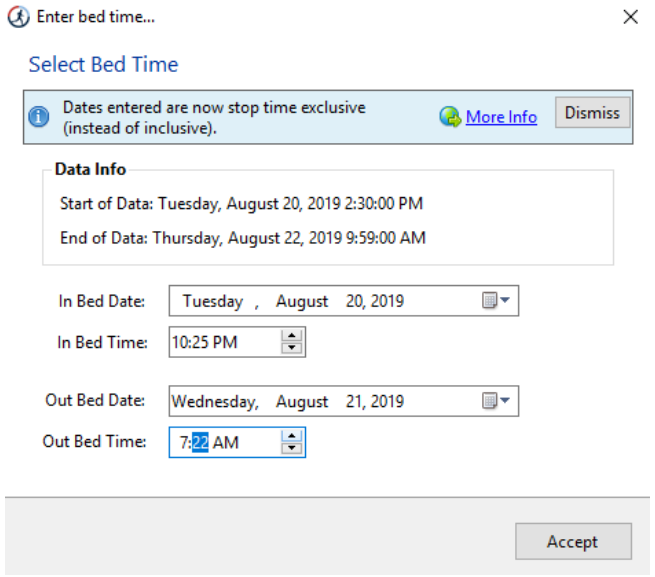
# Sleep

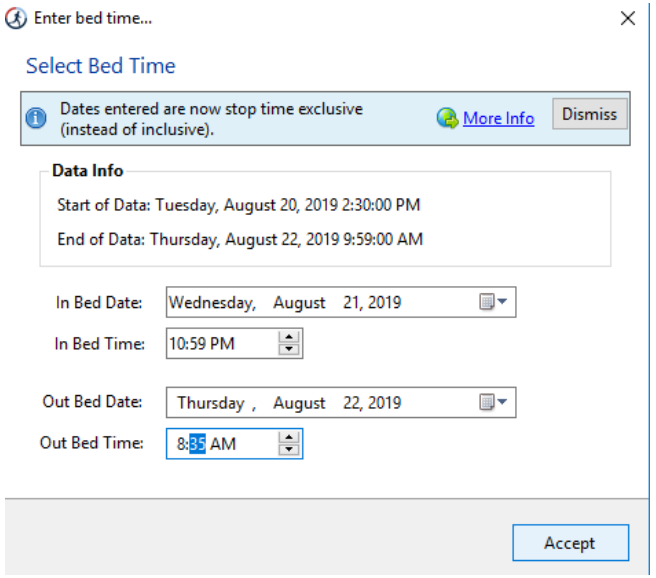
- Select “24hr” to view dataset as it is easier to view sleep periods.
- Ensure “Algorithm” is set to “Cole-Kripke” in top right corner (PMID: 1455130)
  - This algorithm is used to score sleep in adult populations
  - The Sadeh algorithm is used for children and young adults (PMID:7939118)
- Click “Add Sleep Period”



# Entering Sleep Log

- Verifying participants sleep log enter “In Bed Date”, “In Bed Time, “Out Bed Date” and “Out Bed Time”
  - Set each day individually (7 separate days)
  - Example of two days provided
- Click “Accept”

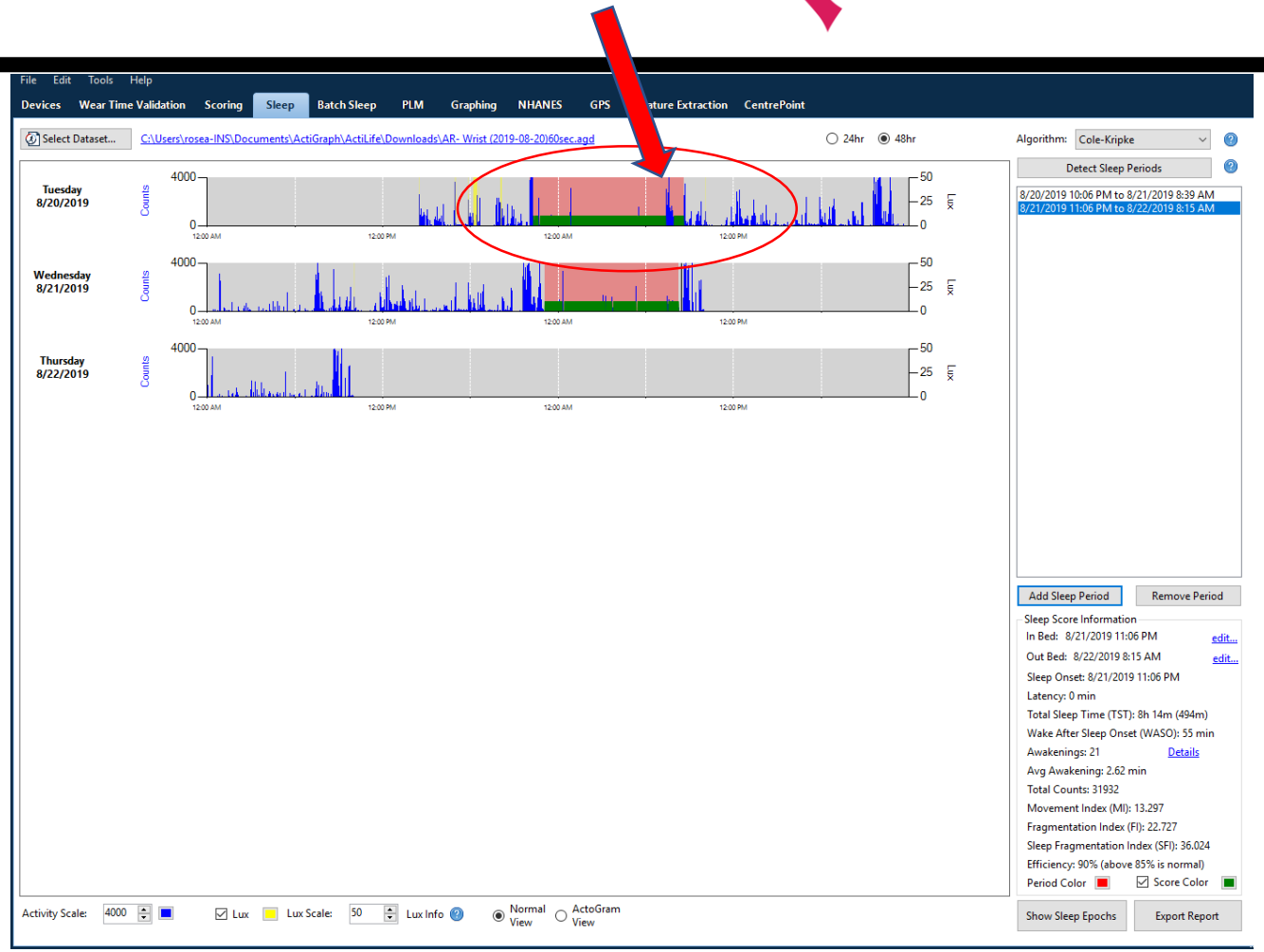


# Incorrect Participant Sleep Log

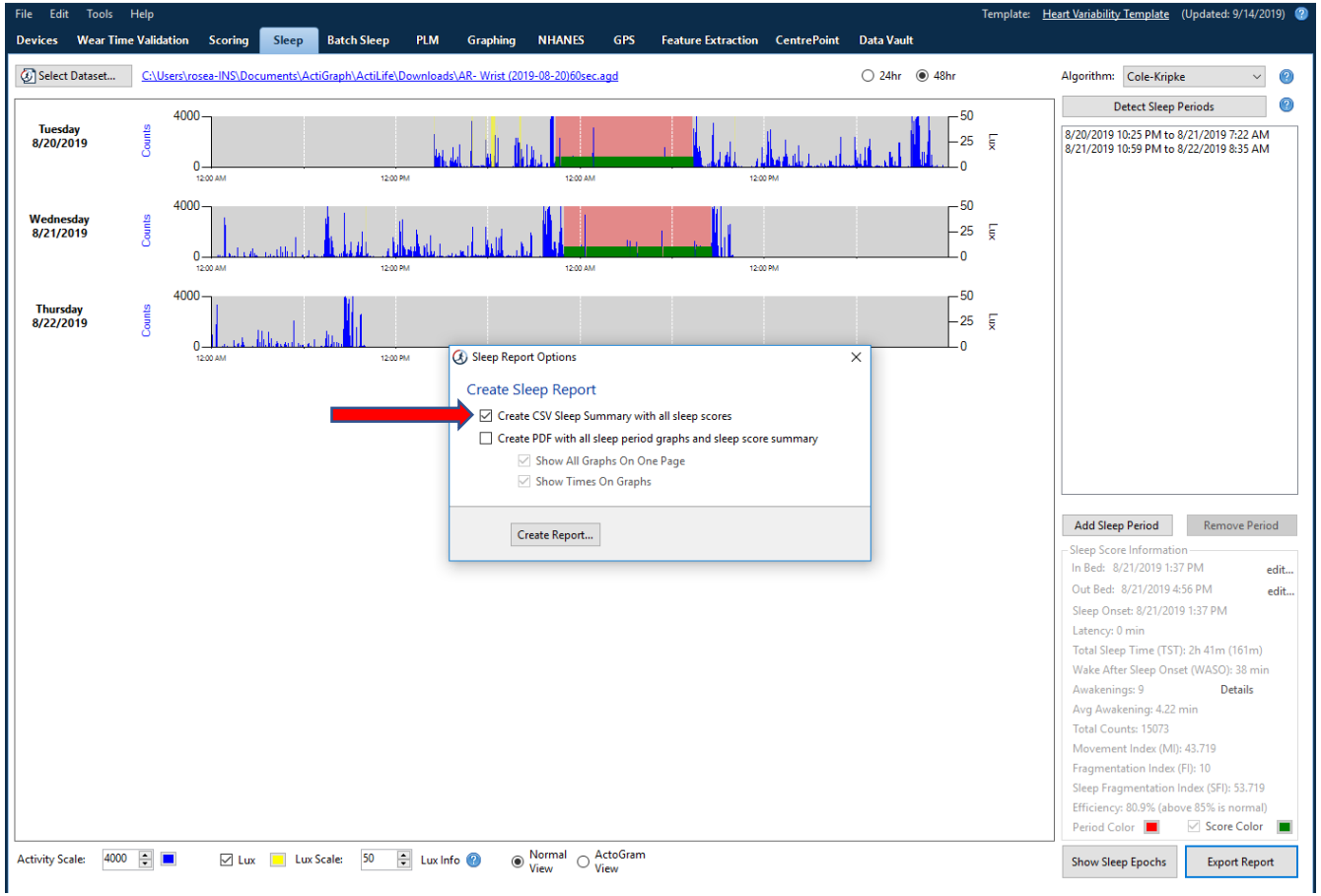
- After entering participants sleep log data, ensure sleep time on graph has little to no movement.
- Provided is a picture of incorrect data measurement of the sleep score.
- If this comes up in entering participant sleep log, please inform Jaqueline or Alex

STOP HERE



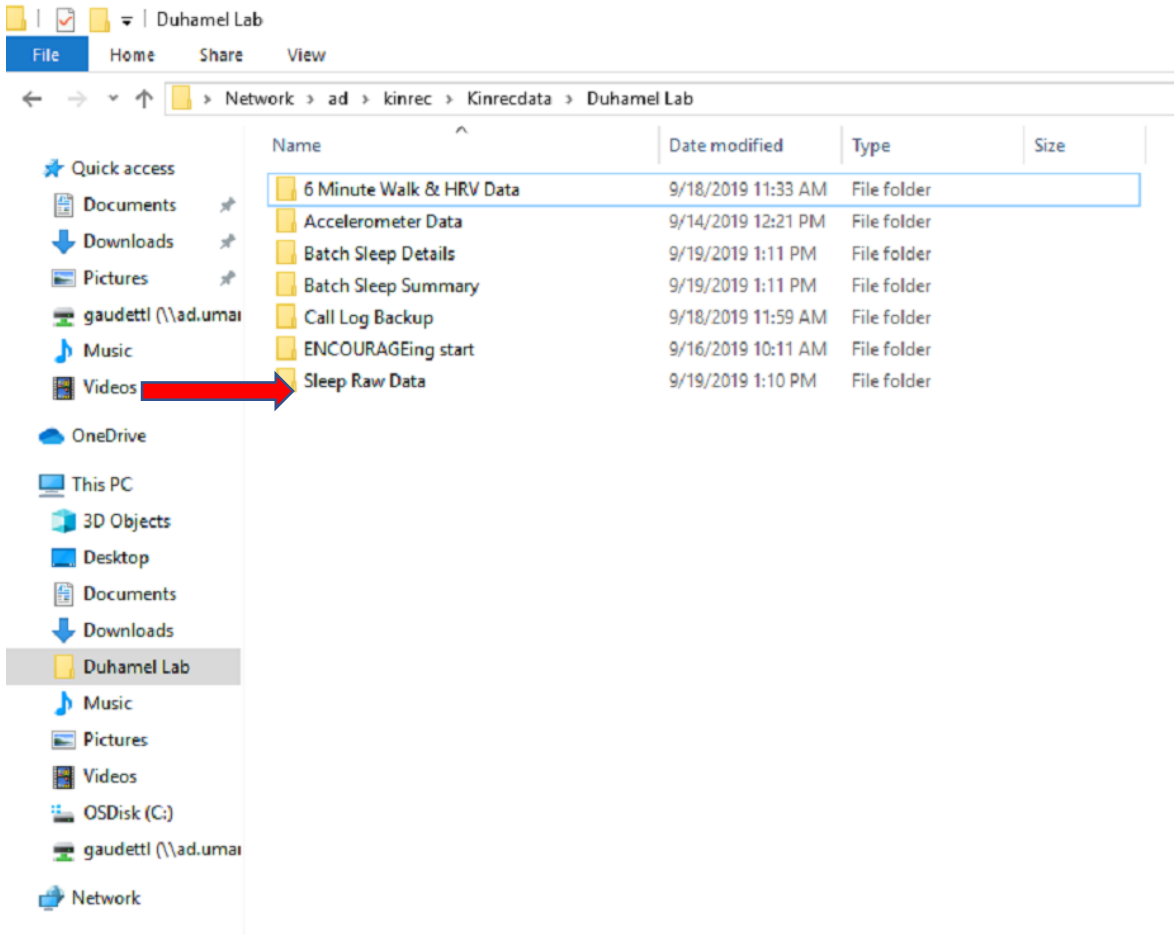
# Exporting Data

- After filling in participants 7 days from their sleep log
- Press Export Report
- “Sleep Report Options” screen will open up
- Click “create CSV sleep summary with all sleep scores
- Unclick “Create PDF with all sleep period graphs and sleep score summary”



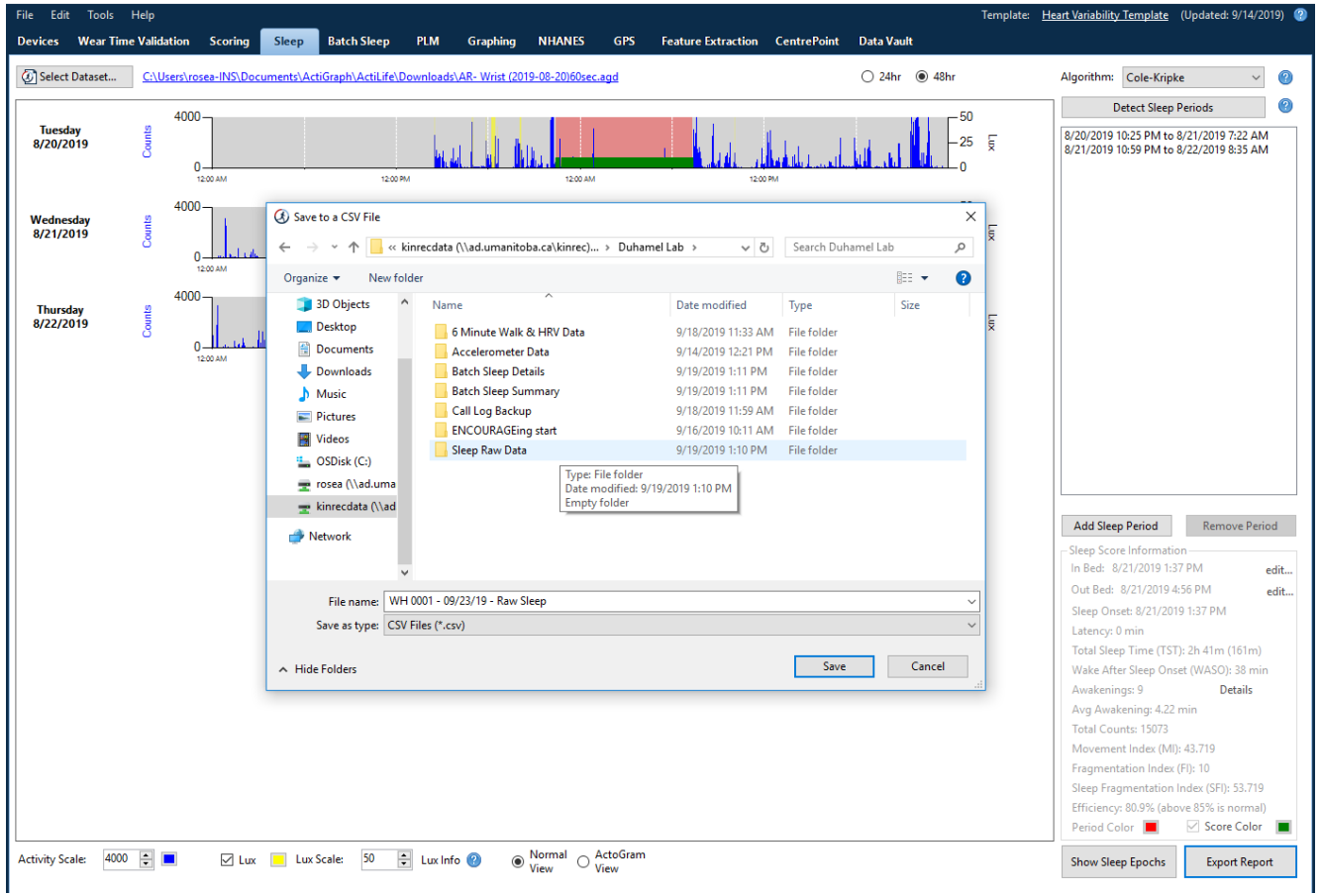
# Saving Raw Data

- Save in “Sleep Raw Data” in the “Duhamel Lab W drive”



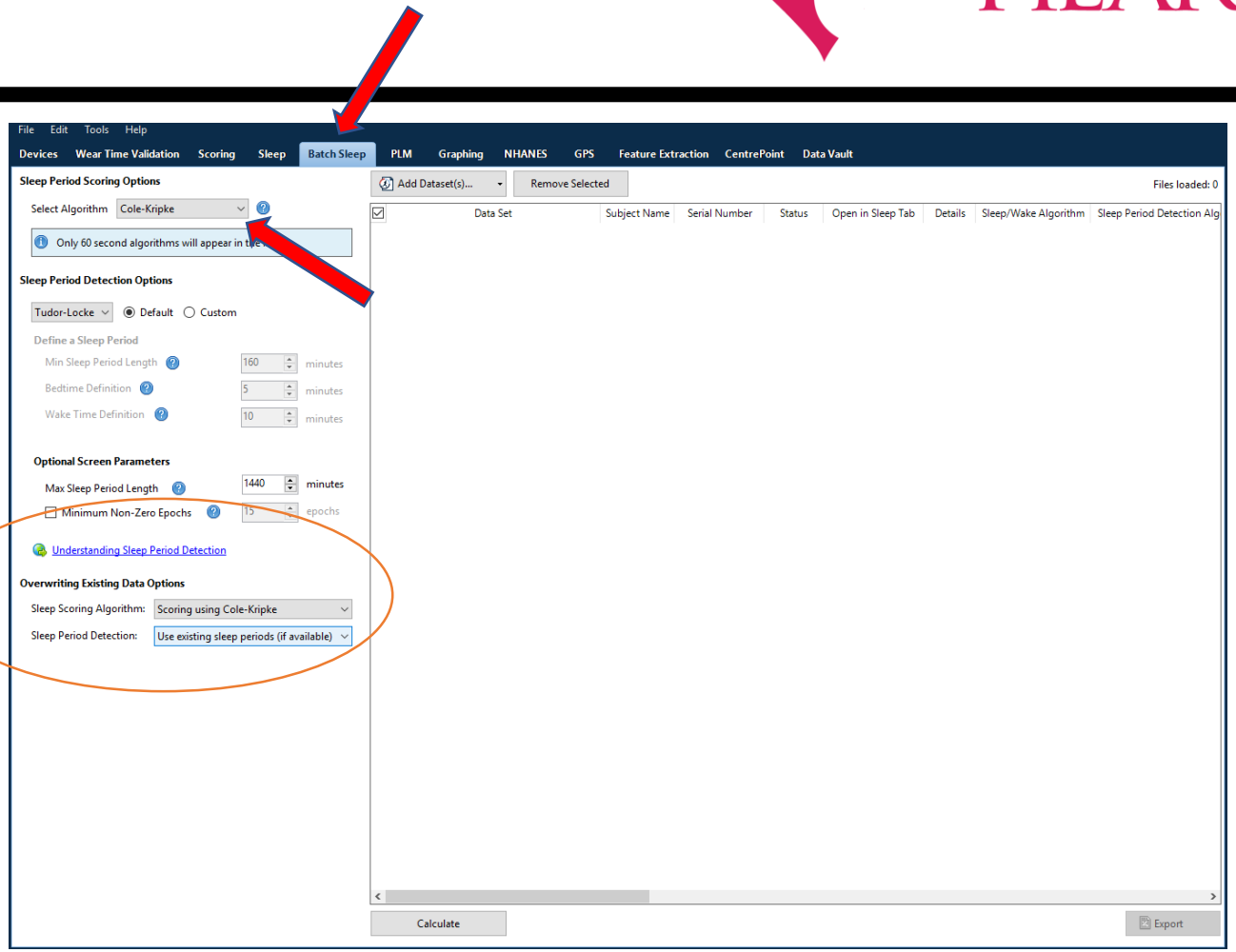
# Saving Raw Data

- In “Sleep Raw Data” folder save file as “WH ID _mm/dd/yyyy _Raw Sleep



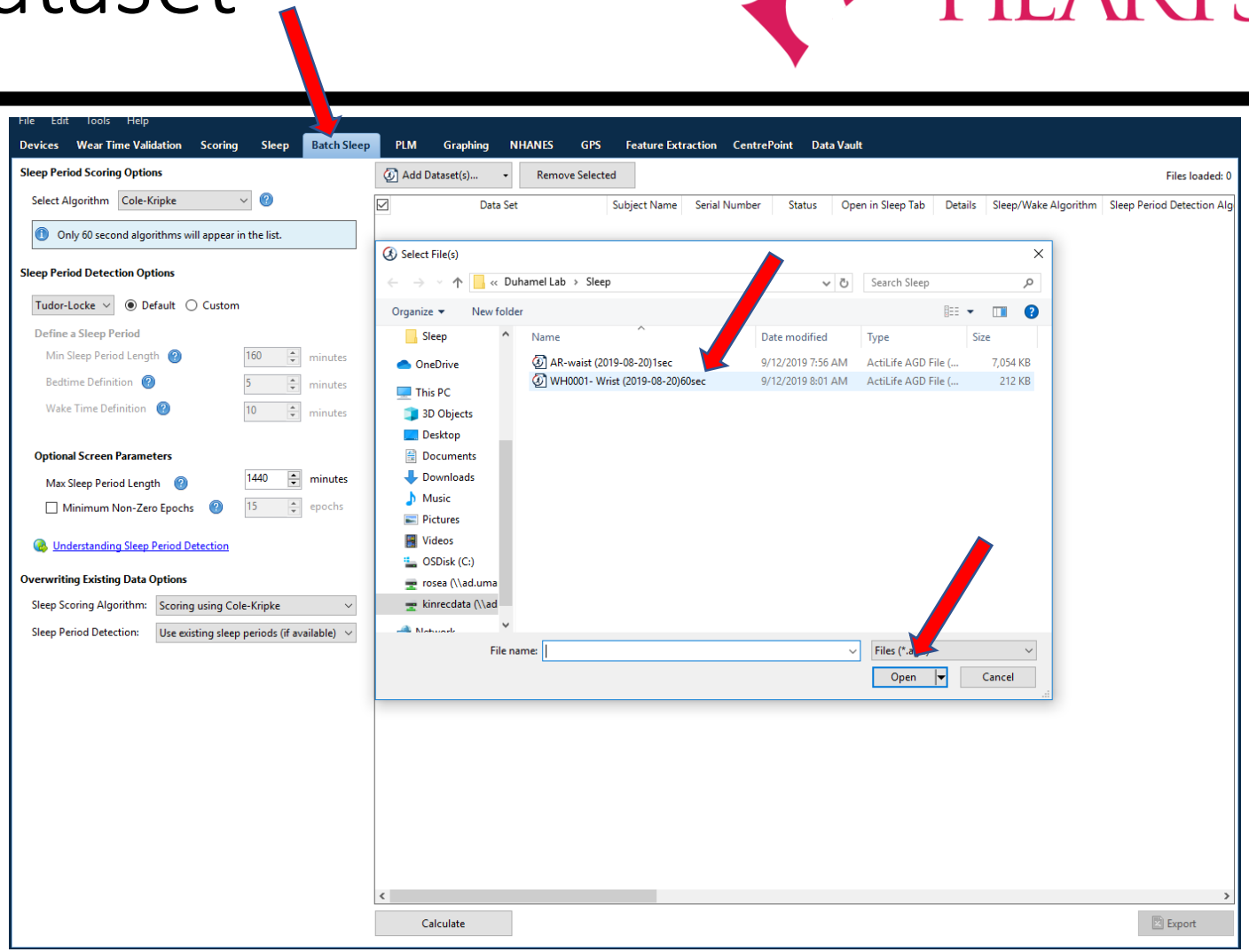
# Batch Sleep Analysis

- Click “Batch Sleep”
- Ensure Algorithm is set to “Cole-Kripke”
- Under “Overwriting Existing Data Options”
  - Sleep Scoring Algorithm is set to “Scoring using Cole-Kripke”
  - Sleep Period Detection is set to “Use existing sleep periods (if available)”



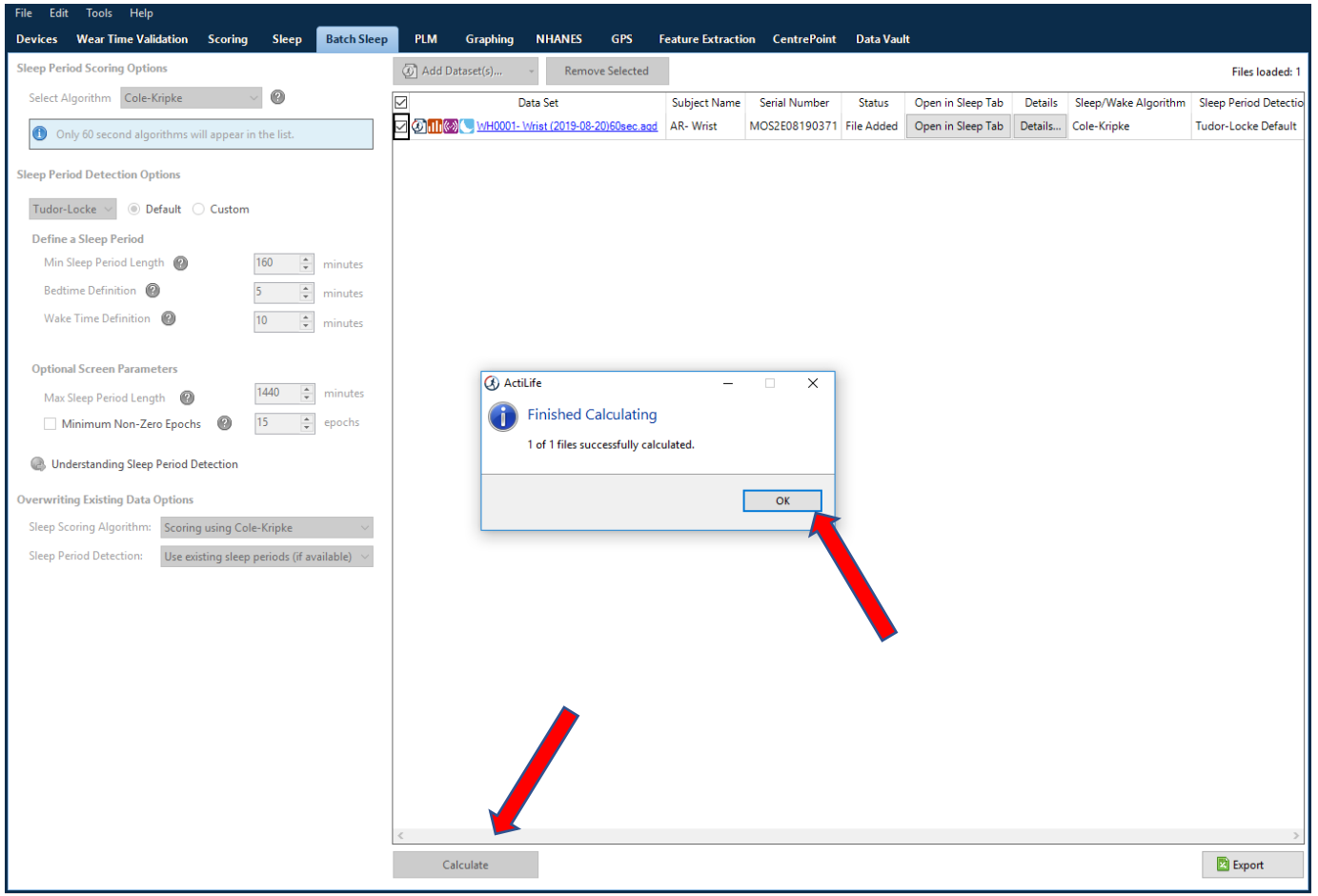
# Batch Sleep: Add Dataset

- Click “Add Dataset”
- Select ““participant ID-Wrist (Date) 60sec”
- Select “Open”



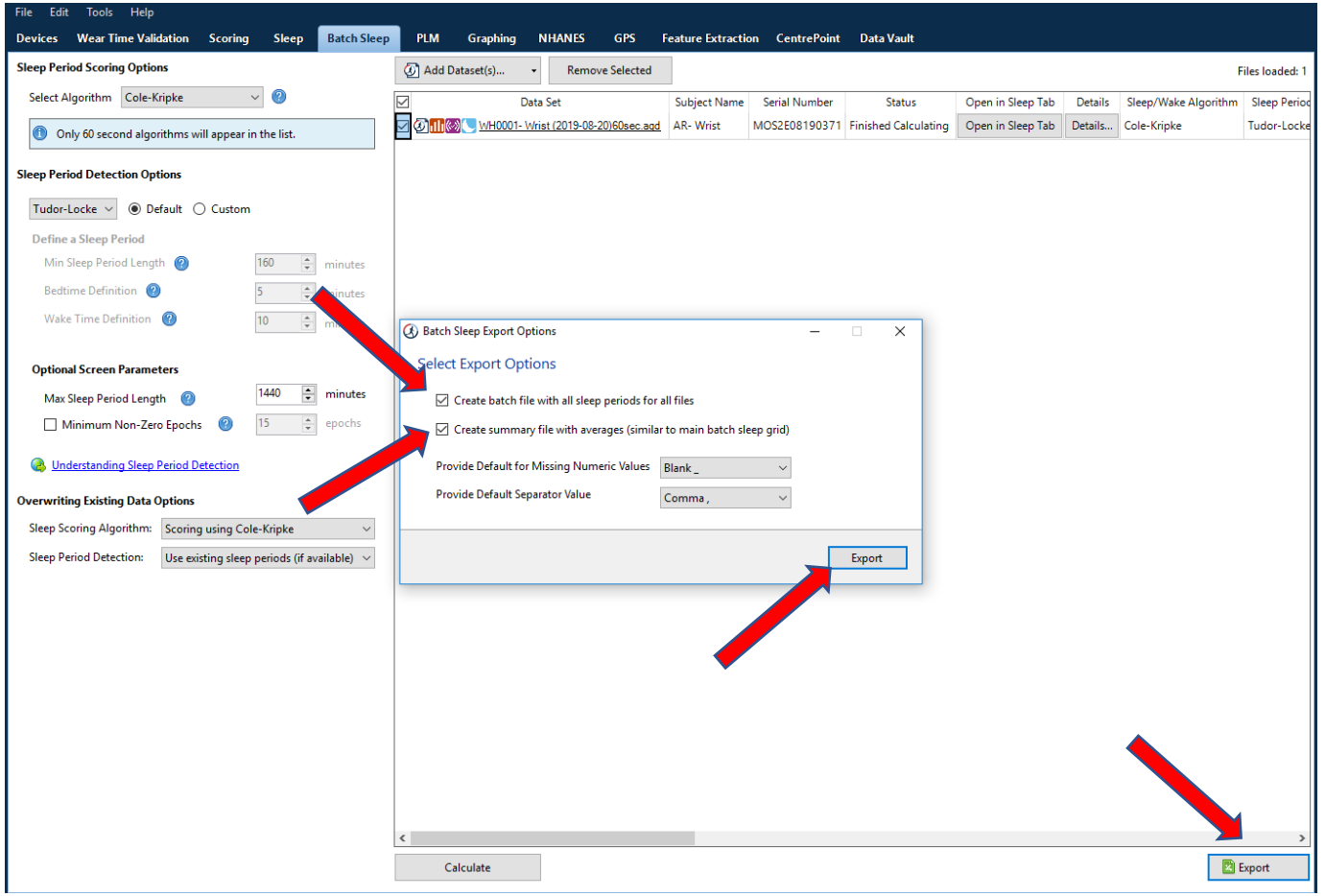
# Batch Sleep: Calculate

- Click “Calculate” and ensure ActiLife is “Finished Calculating”, press “OK”



# Batch Sleep: Export

- Select “Export”
- Select “Create batch file with all sleep periods for all files” box
- Select “Create summary file with averages (similar to main batch sleep grid)” box
- Select “Export”



# Saving Batch Sleep Files

- Select “W drive”, “Duhamel Lab”
- Select “Batch Sleep Summary”
- If you are wanting to view files, press “Open Containing Folder”
- Two files will be saved (Detail and Summary)
  - Detail: Day to Day analysis
  - Summary: Summary of 7 days
- Rename both files, “WHID _date mm/dd/yyyy_BatchSleepDetails or BatchSleepSummary
- Open “Batch Sleep Summary” folder, cut the BatchSleepDetails file and paste into the “Batch Sleep Details” folder