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Sleep, Shiftwork Adaptation, Autonomic Dysfunction, And Metabolic Syndrome

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SLEEP, SHIFTWORK ADAPTATION, AUTONOMIC DYSFUNCTION, AND METABOLIC SYNDROME

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PREFACE

The views expressed in this document are those of the author and do not reflect the official position of the U.S. Army Medical Department Center and School, U.S. Army Medicine, Department of the Army, Department of Defense, or the U.S. Government.

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ABSTRACT

Background: Sleep is considered a physiological necessity and its disruption is associated with a wide variety of adverse mental and physical health outcomes including increased incidence of obesity, cancer, hypertension, cardiovascular disease, type 2 diabetes mellitus, stroke, depression, post-traumatic stress disorder (PTSD), work-related and vehicle accidents, and aberration of the autonomic nervous system. **Methods:** Three studies were conducted from three separate populations. The first study examined the latent trajectories of self-reported sleep quality in active duty Army soldiers over a 3-year period using data from the Global Assessment 2.0 survey and Repeated Measures Latent Class Analysis (RMCLA) procedures. Generalized Estimating Equations (GEE) were then used to compare demographic, military characteristics, and health-behaviors between the resultant latent classes. In the second study, a sample of police officers from Buffalo, New York were used to identify the predominant subgroups of evening and night workers using latent class analysis procedures that characterize adaptation to shiftwork. Generalized Linear Models (GLM) and chi-square tests were utilized to compare demographic, law-enforcement characteristics, and health behaviors between subgroups. In addition, logistic regression was used to develop a risk prediction model for shiftwork adaptation and GLMs were used to compare inflammatory, heart rate variability, and cardiometabolic factors between the subgroups. In the last study, a sample of participants from the Midlife in the United States Study (MIDUS II) Biomarker projects were utilized to examine the relationship between sleep quality,

HRV, and metabolic syndrome. **Results:** In the first study, soldiers with poorer sleep quality trajectories tended to be female, non-white, enlisted, and have non-combat military occupations. Soldiers with persistently better sleep quality had better body composition metrics, physical fitness scores, and were more likely to meet weapon qualification standards. Soldiers in the poorer sleep trajectory groups had lower levels of resiliency across all psychosocial dimensions measured by the GAT 2.0. In the second study, the shiftwork adapted group reported lower probabilities of having a poor response to sleep, stress, and chronic fatigue measures. Additionally, officers in the adapted group were slightly older, had better diets, higher levels of extraversion, agreeableness, hardiness, and lower levels of neuroticism. The adapted group also tended to have more family independence and organization, and less family conflict. There were no differences in inflammatory, HRV, or cardiometabolic risk factors between the latent classes of police officers except for diastolic blood pressure and leptin. In the third paper, there was a negative relationship between poor subjective sleep quality and HRV; an association between poor sleep quality and metabolic syndrome; and an association between low HRV and metabolic syndrome were observed after controlling for relevant covariates. **Discussion:** Sleep has profound effects on physical and mental health. Although there were no significant differences in terms inflammatory, HRV, and cardiometabolic biomarkers between shiftwork adapted and maladapted police officers in our study, our results suggest that the physiological consequences of shiftwork are worse among police officers who are not adapted to shiftwork. Our findings highlight the protentional for interventions such as heart rate variability biofeedback for increasing HRV and sleep quality.

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CHAPTER 1

INTRODUCTION AND SPECIFIC AIMS

1.1 Dissertation Structure

This dissertation encompasses three aims from three separate populations and data sources organized in a manuscript format. Chapter 1 consists of the introduction and specific aims. Chapter 2 describes the background information and rationale for the specific aims. Chapter 2 also will define the three-populations utilized in dissertation to include: Active duty Army soldiers who have completed at least 3 Global Assessment Tool 2.0 surveys between December 1, 2013 and August 31, 2017; police officers from the Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) study in Buffalo, New York; and participants of the Midlife Development in the United States (MIDUS II) Survey and Biomarker projects. Subsequent sections will elaborate on the relationships between the persistence of poor sleep quality, shiftwork adaptation, various psychophysiological and psychosocial risk factors, and clinical outcomes. Lastly, Chapters 3, 4, and 5 will include manuscript formatted sections that address the methods, results, and discussion for each specific aim.

1.2 Specific Aim 1: Trajectories of Self-reported Sleep Quality in Active Duty Army Soldiers

Sleep is considered a physiological necessity, and inadequate or disrupted sleep is associated with a wide range of adverse physical, mental, and behavioral health

outcomes. Sleep disturbance is considered a core component of post-traumatic stress disorder (PTSD), depression, anxiety, and traumatic brain injury (TBI) which are all exceedingly prevalent in military populations. According to the 2016 Health of the Force Report, approximately "23% of soldiers met the Office of the Surgeon General (OTSG) targets for sleep goals and standards."[2] The 2016 Health of the Force report also found that 11% of active duty soldiers have been diagnosed with at least one sleep disorder.[2] Results from a large scale cross-sectional study of US Veterans seeking care at Veteran Health Administration (VHA) facilities over an eleven year period suggests a significant rise in sleep disorder diagnoses between FY2000-FY2010.[3] While the physical and mental health consequences of sleep disruption has been well established, few studies have evaluated the persistence or chronicity of sleep disturbance in military personnel and veterans.[4,5] There is evidence that sleep disturbances may persist after deployments leading to increased risk for anxiety, depression, PTSD, and pain syndromes.[4,6,7] The persistence of sleep disturbance is typically characterized as sleep deprivation or deficiency and is associated with major health risks to include increased risk of cardiovascular disease, cardiovascular disease related morbidity and mortality, hypertension, diabetes mellitus, and several types of cancer.[8]

Using a Repeated Measures Latent Class Analysis (RMLCA) approach, the primary aims of this study were to explore the trajectories of self-reported sleep quality over time among US Army soldiers. This project leveraged the extensive capabilities of the Person-Event Data Environment (PDE), which provides an integrated framework for exploring manpower, personnel, and medical data of Department of Defense (DoD) personnel and their families.[9] The DoD digitizes an ever increasing amount of solider

information that consists of trillions of cells of information.[9] Lastly, the PDE is a secure virtual space where civilian and military researchers can access a longitudinal catalog of over 500 data elements from over 30 DoD sources. For this aim, we utilized information regarding military training, education, demographics, and the Global Assessment Tool (GAT) 2.0. The GAT 2.0 is tool designed to assess soldier's psychological strengths and resiliency.

The specific aims and hypothesizes for Chapter 3 are:

1.2.1 Characterize the predominant trajectories of self-reported sleep quality over a 3-year period in active duty Army soldiers using Repeated Measures Latent Class Analysis (RMLCA) procedures. ***Hypothesis:*** *There are at least two latent trajectory subgroups of active duty Army soldiers who have similar trajectories of subjective sleep quality as defined by the 2-item Pittsburgh Insomnia Rating Scale. Specifically, that at least one group can be characterized as a persistently poor or good sleep trajectory group.*

1.2.2 Incorporate into a risk prediction model a broad range of potentially modifiable and non-modifiable (or potential confounding) risk factors including military occupational specialties, rank, deployment history, and psychosocial factors. ***Hypothesis:*** *Soldiers with persistent poor sleep quality over a 3-year period are more likely to have a combat related military occupational specialty, be of higher rank, have multiple deployments, and negative psychosocial indicators relative to those with persistently better sleep quality.*

1.2.3 Explore linkages between latent subgroup trajectories and various military performance outcomes. ***Hypothesis:*** *There will be a dose-response relationship*

between the latent sleep quality subgroups and various outcomes of military importance to include Army Physical Fitness Test scores and body composition measures.

1.3 Specific Aim 2: Shiftwork Adaptation among Police Officers: The BCOPS Study

It is estimated that upwards of 29% of U.S. worker's schedules are outside of a typical daytime work schedule of 0600-1800.[10] Shiftwork may consist of early morning, evening, night, or rotating shifts. Shiftworkers frequently work in service industries such as healthcare, retail, commercial, and financial industries. Shiftwork is also a critical aspect of military service and law enforcement.[11,12] Previous research has shown shiftwork to be associated with increased incidence of various health conditions including cardiovascular disease, metabolic disorders, gastro-intestinal disorders, and mental health disorders.[13–15] Despite the obvious health effects of shiftwork, there are individuals who appear to tolerate shiftwork better than others. Andlauer and colleagues first introduced the concept of shiftwork adaptation in 1979, and defined it as the ability to adapt to shiftwork without adverse consequences.[16] Currently there is no official definition of shiftwork adaptation or tolerance; however, many operationalize shiftwork adaptation or tolerance as an absence of shiftwork associated fatigue, gastro-intestinal troubles, sleep disruption, or changes in behavior.[17,18]

Metabolic syndrome is an amalgamation of multiple interrelated metabolic and cardiovascular risk factors. Individuals who are overweight, physically inactive, and have genetic a predisposition are at increased risk of developing metabolic syndrome. While, multiple studies have found significant associations between night shiftwork and

metabolic syndrome or its individual components, relatively few have compared and contrasted the health effects among those that are adapted or maladapted to shiftwork.[19–21] The process by which shiftwork effects cardiovascular and metabolic disease risk factors in part is circadian misalignment. Circadian misalignment is characterized by disruption of the 24-hour endogenous circadian system.[22] By identifying the characteristics of adaptation to shiftwork we may be able to develop health strategies that may mitigate the deleterious health effects of shiftwork.

Using a Latent Class Analysis (LCA) approach this study utilized data from the Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) study, which aims to investigate the biological processes by which occupational stressors associated with police work may mediate adverse health outcomes. Data from approximately 430 police officers were utilized for this project. Data elements included information on socio-demographics, self-reported mental and physical health measures, fasting blood samples, a detailed medical history, and various validated questionnaires.[23]

The specific aims and hypothesizes for Chapter 4 are:

1.3.1 To identify the predominant subgroups that characterize adaptation to shiftwork among police officers who are participants of the BCOPS study. ***Hypothesis:*** *There are at least two subgroups of evening and night workers who are not alike in terms of their socio-demographic, occupational, and bio-psychosocial characteristics. Specifically, that at least one group will have a maladaptive response pattern of selected latent class indicator variables.*

1.3.2 Evaluate a broad range of potentially modifiable as well as non-modifiable (or potential confounding) risk factors that may predict shiftwork adaptation among police officers who are participants of the BCOPS study. ***Hypothesis:*** *Age, gender, personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness), hardiness, and measures of poor health (diet, smoking, and physical activity) will predict adaptation to shiftwork among police officers.*

1.3.3 Evaluate the relationship between shiftwork maladaptation and specific cardio-metabolic risk factors, inflammatory biomarkers, and heart rate variability indices among latent subgroups among police officers who are participants of the BCOPS study. ***Hypothesis:*** *Police officers who are maladapted to shiftwork will have poorer/less healthy/unfavorable cardio-metabolic, inflammatory, and heart rate variability profiles.*

1.4 Specific Aim 3: Sleep, Heart Rate Variability, and Metabolic Syndrome

The prevalence of poor sleep, specifically short sleep duration, has increased in conjunction with increased prevalence of metabolic disorders and obesity in United States.[10] Sleep and circadian rhythms play a role in the regulation and optimization of various physiological functions.[12] This suggests a potential relationship between poor sleep and metabolic dysregulation. In a longitudinal analysis of National Health and Nutrition Examination Survey (NHANES) data from 1988-2012, the prevalence metabolic syndrome increased by more than 35% among adults.[24] In a meta-analysis evaluating the relationship between sleep duration and metabolic syndrome, the pooled odds ratios (OR) for metabolic syndrome among those with sleep duration <7 hours was 1.23 (95% CI: 1.11–1.37, p<0.001) compared to individuals with daily sleep duration of

7-8 hours .[25] They also found a dose response relationship with decreasing sleep duration of <5, 5-6 hours, and 6-7 hours respectively.[25] Multiple cross-sectional studies examining self-reported sleep quality have found associations between poor sleep and metabolic syndrome and its components; however, due to the cross-sectional nature of the study designs no causal relationship between poor sleep and metabolic syndrome could be evaluated.[26–28]

The final study utilized data from the Midlife Development in the United States (MIDUS II) survey and biomarkers projects. Approximately 966 participants who had complete heart rate variability, metabolic syndrome, and sleep data quantified by Pittsburgh Sleep Quality Index (PSQI) were used to examine relationships between poor sleep quality, heart rate variability, and metabolic syndrome. Lastly, we examined whether heart rate variability acts as a moderator in the relationship between poor sleep quality and metabolic syndrome.

The proposed specific aims and hypothesizes for Chapter 5 are:

1.4.1 Examine the cross-sectional associations between poor sleep quality, low heart rate variability, and metabolic syndrome in a nationally representative sample of US Adults from the Midlife Development in the United States Study. ***Hypothesis:*** *Participants with poorer sleep quality will have lower heart rate variability compared to participants with good or normal sleep quality measures. Participants who meet the criteria for metabolic syndrome will have poorer sleep quality compared to participants who do not meet the criteria for metabolic*

syndrome. Participants with poor sleep quality and low heart rate variability will have increased odds of metabolic syndrome.

1.4.2 Evaluate to what extent heart rate variability moderates the relationship between sleep quality and metabolic syndrome. ***Hypothesis:*** *The relationship between sleep quality and metabolic syndrome is moderated by, to some extent, heart rate variability.*

CHAPTER 2

BACKGROUND

2.1 Sleep

Adverse health effects of poor sleep

Sleep is considered a physiological necessity and its disruption is associated with a wide variety of adverse mental and physical health outcomes including increased incidence of obesity, cancer, hypertension, cardiovascular disease, type 2 diabetes mellitus, stroke, depression, post-traumatic stress disorder (PTSD), and accidents.[8,29–31] Sleep disruption also is associated with higher healthcare costs, increased mortality, increased morbidity, and decreased quality of life.[8,32–34] Sleep disturbance can be characterized as insomnia, short sleep duration, or nightmares and is particularly prevalent among U.S. service members.[31] According to the 2016 Health of the Force Report, only "23% of soldiers met Office of the Surgeon General (OTSG) targets for sleep goals and standards."[2] The 2016 Health of the Force report also found that 11% of active duty soldiers have been diagnosed with at least one sleep disorder.[2]

Besides being independently associated with various health outcomes, sleep disturbance is a core component of post-traumatic stress disorder (PTSD), depression, anxiety, and traumatic brain injury (TBI) which are exceedingly prevalent in military populations.[31] Research also suggests that for many service members sleep disturbance persists after deployments despite having adequate time for reintegration and recovery; however, the factors that contribute to the persistence of sleep disturbance have not been

fully characterized. In addition to multiple deployments the symptoms of sleep disturbance are also exacerbated by hazardous working conditions, inconsistent work hours, routine exposure to loud noises and lights, and crowded sleeping spaces.[5] Deployments are also associated with circadian rhythm disturbances, sleep deprivation, prolonged sleep latency, and increased wakening after sleep onset.[5,35] In a 2013 study exploring sleep disorders and medical comorbidities in active duty military personnel, Mysliwiec et al. found substantially higher prevalence of short sleep duration compared to non-military populations.[7] Wesensten et al. found that short sleep duration is linked to compromised mental and physical heath and cognitive impairment.[36]

Persistence or chronicity of poor sleep

The persistence of sleep disturbance is thought to be a more appropriate predictor of poor health and chronic disease. In a 3-year follow-up of participants with insomnia from the Twenty-07 Study, those with more severe insomnia symptoms demonstrated greater persistency of insomnia symptoms.[37] In a prospective cohort study of middle-aged and elderly men and women in West Scotland, Green et. al found that insomnia is more likely to proceed into chronicity in older individuals, women, and those with manual labor occupations.[38] Longitudinal studies exploring persistent insomnia symptoms suggest a population prevalence ranging from 40-70%.[37–41] Results from a large scale cross-sectional study of U.S. Veterans seeking care at Veteran Health Administration (VHA) facilities over an eleven year period suggests a significant rise in sleep disorder diagnoses between FY2000-FY2010.[3] A 2013 longitudinal study evaluating sleep duration trajectories in the general population found a prevalence of 11% for short sleep trajectory (<6 hrs) groups and ~2% for long sleep (≥9 hrs) group with a slight downward

trend of sleep duration.[42] Additionally, they found that age, sex, and subject sleep quality were predictors of latent class membership.[42]

Few studies have evaluated the persistency or chronicity of sleep disturbance in military personnel and veterans; however, there is some evidence that sleep disturbances persists after deployments.[4,6] In a retrospective cohort that aimed to explore to sleep disruption among different combat injury categories among recently redeployed soldiers Capaldi and colleagues found that the rates of obstructive sleep apnea, excessive awakenings, daytime sleepiness, and hypoxia from polysomnographically (PSG) were high in the full sample; however, there were no differences among combat injuries.[4] Lastly, in a study examining the relationship between self-reported sleep quality measures and indicators of resilience in a US military population, military personnel with insomnia symptoms had lower odds of (Odds Ratio = 0.73, 95% Confidence Interval = 0.68-0.78) deploying.[6] In another study investigating the temporal stability of different patterns of insomnia suggests that subdividing insomnia into various categories according to symptomatology may not be the most appropriate in for evaluating sleep quality overtime.[43] Specifically, they found that patterns of insomnia symptoms showed low stability; however, it should be noted that the observation time was only 4 months.[43]

2.2 Metabolic Syndrome

In the Third Report of the National Cholesterol Education Program (NCEP III), metabolic syndrome is characterized as a clinically significant group of metabolic risk factors associated with an increased risk of coronary heart disease. Individuals who are overweight, physically inactive, or have a genetic predisposition are at increased risk of developing metabolic syndrome. Metabolic syndrome is generally characterized by

abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and insulin resistance or glucose intolerance.[44] The diagnostic criteria for metabolic syndrome varies according organization; however, the NCEP III defines metabolic syndrome as the presence of three of the following metabolic risk factors: waist circumference >102cm for men and >88cm for women; triglycerides ≥150 mg/dL, HDL cholesterol <40 for men and <50 for women; blood pressure ≥130/85; or serum glucose ≥110 mg/dL.[44]

2.3 Shiftwork

It is estimated that upwards of 29% of U.S. workers have jobs that occur outside of a typical daytime work schedule of 0600-1800. [10] Shiftwork may also consist of early morning, evening, night, or rotating shifts. Shiftworkers frequently work in service industries such as healthcare, as well as numerous other high-consequence occupations (e.g., military, emergency response, transportation, public utilities).[11]

Adverse health effects of shiftwork

Frequent shiftwork is a known disruptor of normal sleep-wake cycles and frequently leads to short sleep duration, excessive fatigue, metabolic dysfunction, and cognitive impairment.[45] In an review of 38 meta-analyses and 24 systematic reviews Kecklund et al., found compelling evidence that shiftwork is associated with an increased risk for breast cancer, coronary heart disease, and various other chronic health conditions.[45]

The consequences of shiftwork extend beyond the development of chronic health conditions to include work-related accidents and increased rates of absenteeism and lost work days.[11] In an evaluation characterizing the job attitudes and health perception in a

military sample, Demerouti et al. found that soldiers working outside of traditional work shifts reported significantly greater work-family conflicts.[46]

Shiftwork and sleep

It is estimated that upwards of 20% of shiftworkers report short sleep duration and excessive sleepiness.[47] Unfortunately, systematic reviews evaluating the relationship between sleep quality and shiftwork are scant; however, the available literature does support evidence that sleep periods that end in the early morning or after a night shift demonstrate short sleep onset latency, fewer awakenings, and non-restorative sleep.[48,49] In a 2015 study, Linton and colleagues conducted a systematic review and meta-analysis that characterized the effects of shiftwork on sleep quality in epidemiological studies.[50] Overall, they found that shiftworkers are at an increased risk for chronic sleep disturbance.[50]

A defining aspect of shiftwork is the requirement that shiftworkers sleep at a time outside their normal circadian alignment.[45,51] The miss-alignment of circadian rhythms leads to adverse health conditions and sleep disturbance.[48,52,53] Sleep problems reported by shiftworkers are typically described as excessive sleepiness that occurs during night work, early morning shifts, or when there is inadequate recovery time between shifts. The amount of time needed for a shiftworker to recover between shiftwork is poorly understood. When sleep problems in a shiftworker persists for at least 3 months, a shiftworker may fulfil the diagnostic criteria for Shift Work Sleep Disorder (SWSD). The criteria for SWSD is classified in the International Classification of Sleep Disorders (2nd edition) and includes: persistent or recurrent patterns of sleep disturbance primarily attributed to circadian disruption or misalignment; circadian-related sleep disruption

leading to excessive daytime sleepiness or insomnia; and sleep disturbance that contributes to social and occupational impairment.[54] The literature exploring SWSD alludes to a potential relationship between SWSD and poor health outcomes, sleep disturbance, and work-related problems; however, the majority of literature is cross-sectional making it difficult to make causal interpretations.

Shiftwork and metabolic syndrome

To date multiple studies have compared the metabolic dysregulation between day and shiftworkers; however, results have been in consistent.[55–57] This is most likely due to variability in study design and use of potential confounders. Furthermore, there is little consistency in the way shiftwork is defined and there are multiple criteria for which metabolic syndrome is defined. In a 2015 meta-analysis that evaluated shiftwork and diabetes in observational studies, Y. Gan et al. found a pooled adjusted odds ratio (OR) for shiftwork and diabetes mellitus of 1.09 (95% Confidence Interval (CI) = 1.05 – 1.12), with stronger associations demonstrated in men compared to women.[21] M. Vyas et al. found in their systematic review of shiftwork and vascular events a risk ratio of 1.24 (95% CI 1.10-1.39) for the association between shiftwork and a coronary event.[19] Drongelean et al. found in their review a crude association between shiftwork and increased body weight; however, many of the evaluated studies were not appropriately adjusted for relevant confounders.[20] In another systematic review investigating the association between shiftwork and metabolic syndrome found no sufficient evidence for an association between shiftwork and metabolic syndrome after controlling for relevant confounders.[15]

In a prospective study exploring night shiftwork and metabolic syndrome, Pietroisusi et al., found an relative risk (RR) of 5.0 (95% CI 2.1-14.6) when comparing night shiftwork to day shiftworkers.[58] In an evaluation to confirm the association between shiftwork and risk of developing metabolic syndrome, Tucker et al, reported an adjusted OR of 1.78 (95% CI 1.03-3.08) and that individuals who worked rotating shifts were more likely to have metabolic syndrome, with an adjusted OR of 1.96 (95% CI 1.03 – 3.75).[59] A systematic review and meta-analysis of 34 studies, Vyas et al., found that shiftwork was associated with myocardial infarction and ischemic stroke.[19]

Shiftwork adaptation

Andlauer et al., first introduced the concept of shiftwork tolerance in 1979.[16] They surmised that the absence of problems usually associated with shiftwork were a consequence of a complex interaction of behavioral and biological predispositions.[16] Shiftwork tolerance is often referred to as shiftwork hardiness or adaptation in the literature. Despite an abundance of literature characterizing shiftwork tolerance there is currently no widely accepted definition of shiftwork tolerance; however, most definitions include measurements of health-related quality of life, social problems, mental health, alcohol tendency, and sleep-related disorders.[60] In exploratory factor analysis, Saksvik-Lehouillier et al, found that measures of well-being and physical health were the most important constructs of shiftwork tolerance.[61]

It is unclear as to whether the aberrations to physical and mental health associated with shiftwork is caused by chronic circadian misalignment, the physiological disruption of homeostasis, or the unhealthy coping mechanisms associated with shiftwork.[62] In a study that aimed to characterize shiftwork related attitudes, behaviors, and coping

strategies, Burch et al., found that factors associated with optimal work performance include adequate sleep, evening chronotype, increased age, and organizational satisfaction.[62] In a systematic review of 60 articles, Saksvik et al., found that young age, male gender, evening chronotype, increased flexibility, and low neuroticism were associated with higher shiftwork tolerance.[18]

Additionally, while shiftwork is associated with poor sleep quality, several studies have also examined relationships between negative work-related stressors and poor sleep quality. Negative work-related stressors include high job demand and strain and lack of organizational support.[63–68] Furthermore, positive work-related factors such as social support, job control, and organizational justice or support have positive associations with sleep quality.[63] In a study examining the effects of work stress on subjective sleepiness found that higher perceived stress during work was characterized by increased sleepiness and sleep disturbance compared to low stress weeks.[66] In another study (n=1,209) assessing the effect of job strain and control found that increased job strain increased the odds (OR=2.4, 95% CI 1.3-4.0) of insomnia symptoms; whereas, job control decreased the odds (OR=0.5, 95% 0.3-0.8) of insomnia.[65]

In a study of 740 Dutch police officers found that, officers classified as intolerant to shiftwork had more severe health related complaints, and that tolerance to shiftwork was primarily related to subjective sleep quality, need for recovery, fatigue, and work-life balance.[51] In another study of police officers, that aimed to assess the criteria for shiftwork tolerance and investigate the relationship between personality traits and shiftwork tolerance found that shiftwork tolerance was associated with personality and

traits and mood states.[69] Specifically, that police officers with high anxiety trait and negative or repressive mood were less likely to demonstrate tolerance to night work.[69]

There is also evidence that there is an genetic interaction between circadian genes and individual sleep patterns that play a significant role in tolerance to shiftwork.[70–73] Findings from a genome-wide association study (GWAS) conducted by Sulkava et al., suggests that genetic variant near MTNR1A may be associated with job-related exhaustion through biological mechanism that leads to reduced melatonin signaling in the brain.[74] A 2015 study that aimed to examine whether night-shiftworkers who carry the five-repeat variant of the PERIOD 3 gene concluded that carrier of the five-repeat PERIOD 3 had significantly higher levels of sleepiness occurring during overnight work hours and earlier circadian phases that suggest maladaptation to shiftwork.[70]

Besides psychosocial, work-related stressors, personality, and mood states age and gender are also considered important predictors of shiftwork adaptation or tolerance.[18] Results from a 2011, systematic review found that most studies related young age to tolerance to shiftwork.[18] Furthermore, age 40-50 represents a critical transition to increased likelihood of being intolerant to shiftwork.[75,76] A potential explanation for aging effect is that older individual may be more sensitive or have lower ability to tolerate circadian misalignment.[77] Additionally, female gender appears to be a predictor of tolerance to shiftwork; however, there is less consensus regarding the direction and strength of the association.[18] However, in a systematic review conducted by Saksvik and colleagues found that the majority of studies favored male gender as a predictor of shiftwork tolerance.[78]

2.4 Heart Rate Variability

Heart rate variability (HRV) describes the variability in time between consecutive heart beats or R to R intervals. HRV is typically quantified using time or spectral domain procedures. Time domain measures are derived from R to R intervals by measuring the time between consecutive R wave peaks of the heartbeat waveform obtained via electrocardiography. The most commonly presented time domain measures include root mean square of successive differences (RMSSD), standard deviation of average RR interval (SDRR), and the HRV triangular index.[79,80] Spectral Domain measures are classified as low (LF) or high-frequency (HF) activity and provide insight into autonomic nervous system (ANS) activity. HF-HRV is thought to represent parasympathetic influences, while LF-HRV represents influences of both the sympathetic and parasympathetic inputs.[81,82]

Heart rate variability and sleep

A potential physiological mechanism that may explain the relationship between sleep quality and poor health outcomes is the aberration of the autonomic nervous system (ANS). Aberration of the ANS can be classified as greater sympathetic activation or parasympathetic suppression. Previous studies have shown that norepinephrine, epinephrine, heart rate, and blood pressure are lower during periods of sleep.[83,84] While high HRV is associated with greater vagal inhibitory tone, low HRV is associated with undifferentiated sympathoexicitatory influences.[85] This pathway connects the prefrontal cortex and autonomic output regions thus influencing heart rate and subsequently HRV.[85]

Sleep is primarily a function of the ANS and provides a great opportunity to explore HRV. Stein and colleagues explored heart rate and HRV changes during the different stages of sleep and found that heart rate is decreased in association with decreased variability in subsequent sleep stages.[82] Wakefulness states are characterized by an increase in SNS or a decrease PNS activity, and states of relaxation are characterized by an increase in PSN activity.[86] Whitehurst et al. presented the first in terms of quantitative evidence that the ANS plays a role in memory consolidation during sleep. Sleep plays a vital role in consolidation of stable long-term memories.[87] Slow wave sleep in particular demonstrates higher PNS activities compared with wakefulness and REM sleep.[87] Elevated HF HRV has been associated with increased cognitive performance, greater working memory, and attention.[87]

A relatively small number of studies have examined HRV among individuals with poor and good or normal sleep. In an age, sex, weight-matched study of insomniac patients and controls, Bonnet and colleagues found increased low frequency power and decreased high frequency power in insomniacs compared to healthy controls.[88] In another study examining insomnia and healthy-controls matched individuals found decreased HRV coherence among insomniacs compared to controls.[89]

2.5 Heart Rate Variability and Metabolic Syndrome

The components of metabolic syndrome have been previously evaluated and have been shown to be individually associated with lower HRV.[90–92] In an evaluation of whether multiple components of metabolic syndrome are associated with low HRV, Liao et al., found that HRV indices were significantly lower in individual with multiple components of metabolic syndrome.[93] They also found HRV indices decreased

significantly as the number of metabolic syndrome components increases. [93] Min et al., found that Korean adults with metabolic syndrome had lower mean levels of HRV, and all components of metabolic syndrome were negatively correlated with HRV indices.[94]

2.6 Person-Event Data Environment

The Person-Event Data Environment (PDE) was originally created to merge various Department of the Army and Department of Defense (DoD) data sources, and provides an integrated framework for exploring manpower, personnel, and medical data of DoD personnel and their families.[9] The DoD continuously endeavors to manage a large volume of administrative data for purpose of analyses with policy implications. Thus the DoD digitizes an ever increasing amount of solider information that consist of trillions of cells for information. [9] The PDE is a secure virtual space where civilian and military researchers can access a longitudinal catalog of over 500 data elements from over 30 DoD.

The Global Assessment Tool (GAT) 2.0. The GAT 2.0 is a tool designed to assess soldier's psychological strengths and resiliency in conjunction with the US Army's Comprehensive Solider and Family Fitness (CSF2) program.[95] The GAT 2.0 is a survey required annually by all members of the US Army who are not currently deployed to a combat zone. The four primary dimensions of social, emotional, spiritual, and family fitness were originally derived from the World Health Organization primary dimension of the health.[96]

2.7 Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) Study

The BCOPS study was a population-based cohort study that aimed to investigate the associations of occupational stressors with the psychological and physiological health

of police officers.[23] A total of 710 police officers who worked with Buffalo, New York Police Departments were invited to participate in the study of which 464 officers agreed to participate and were examined between June 4, 2004 and October 2, 2009. Multiple studies been published from the BCOPS cohort examining the effects of police work on wide range of health-related outcomes such as stress, sleep, and metabolic derangement.[97–99]

2.8 Midlife in the United States (MIDUS) Study II

The original MIDUS study was initiated by a multidisciplinary team of subject matter experts interested in the influence of psychosocial factors on the health of early aged adults to later life.[100] The initial sample of the MIDUS study included a sample of continental U.S. residents who were enrolled between 1995 and 1996. The MIDUS II study is a longitudinal follow-up from the first MIDUS study that aims to investigate the long-term role of behavioral, psychological, and social factors in age associated physical and mental health outcomes. The MIDUS II survey assessed a subsample of the original respondents to ascertain the biopsychosocial pathways that contribute to physical and mental health metrics. The MIDUS II biomarker project collected an extensive number of biomarkers and health assessments from a sample of 1,255 adults.

CHAPTER 3

TRAJECTORIES OF SELF-REPORTED SLEEP QUALITY IN ACTIVE DUTY ARMY SODLIERS[1]

[1] Nevels, T., M. Wirth, A. Mclain, JP. Ginsberg, J.B. Burch. To be submitted to *Chronobiology International*, *Sleep*, or *Journal of Military Medicine*.

3.1 Abstract

Introduction. Sleep disturbance is considered a core component of post-traumatic stress disorder (PTSD), depression, anxiety, and traumatic brain injury (TBI) which are all exceedingly prevalent in military populations. According to the 2016 Health of the Force Report, only "23% of soldiers met the Office of the Surgeon General (OTSG) targets for sleep goals and standards." Sleep disturbance is a predictor of poor mental health, chronic disease, and increased mortality risk; however, the factors that contribute to persistent sleep disturbances are not well characterized, particularly among military personnel. **Objectives.** (1) Characterize the predominant trajectories of self-reported sleep quality over a 3-year period in active duty U.S. Army soldiers using repeated measures latent class analysis (RMLCA) procedures; (2) Identify factors that predict latent class membership including potentially modifiable and non-modifiable risk factors (e.g., rank, deployment history, and psychosocial factors); (3) Explore linkages between latent subgroup trajectories and various measures of military performance to include Army physical fitness test scores, body composition metrics, and weapon qualification standards. **Methods.** The study population consisted of a nationally representative sample of 127,348 U.S. Army active duty soldiers who have completed at least three Global Assessment Tool 2.0 surveys between December 31, 2013 and August 31, 2017. A repeated measures latent class analysis was then used to identify latent trajectory subgroups using the 2-item Pittsburgh Insomnia Rating Scale (PIRS-2). Resultant latent classes were comparted using generalized estimating equations for repeated measures to identify characteristics that differed among the latent trajectory subgroups. **Results.** Based on interpretability, model parsimony, and goodness of fit statistics a three-class

model was chosen that consisted of progressively worsening sleep trajectories: good (n=18,962; 16%) moderate (n=83,879; 62%), and poor sleepers (n=24,507; 27%). Soldiers belonging to the poor-sleep trajectory group tended to be slightly older (>30 years of age) (48%) compared to those in the good (46%) or moderate (45%) groups. A higher proportion were female (19%), black (27%), married (60%), and had less than a college education (76%) compared to the good or moderate sleep groups. Additionally, poor-sleepers were more likely to be enlisted (86%) and have a support related (78%) military occupation specialties (MOS); whereas, good sleepers tended to be officers or warrant officers. Among the psychosocial fitness dimensions evaluated, members with poor sleep trajectories had lower levels of emotional, social, family, and spiritual fitness scores relative to soldiers in the better sleep quality trajectory groups. **Discussion.** A substantial proportion of US active duty Army soldiers reported persistently poor sleep quality over a three-year period. The establishment of public health initiatives focused on soldiers at risk for transitioning to persistent poor sleep quality may lead to reductions of various psychological and medical conditions as well as improve overall military performance.

3.2 Introduction

Sleep is considered a physiological necessity and its disruption is associated with a wide variety of adverse mental and physical health outcomes including increased incidence of obesity, cancer, hypertension, cardiovascular diseases, type 2 diabetes mellitus, stroke, depression, post-traumatic stress disorder (PTSD), and work-related and motor vehicle accidents.[8,29–31] Poor sleep also is also a predictor for cardiovascular disease associated and all-cause mortality.[101–103] Additionally, sleep disturbance also is

considered a core component of PTSD, depression, anxiety, and traumatic brain injury (TBI) which are all exceedingly prevalent in military populations. According to the 2016 Health of the Force Report, only "23% of soldiers met the Office of the Surgeon General (OTSG) targets for sleep goals and standards."[2] The 2016 Health of the Force report also found that 11% of active duty soldiers have been diagnosed with at least one sleep disorder.[2] Results from a large scale cross-sectional study of U.S. Veterans seeking care at Veteran Health Administration (VHA) facilities over an eleven year period suggested a significant rise in sleep disorder diagnoses between FY2000-FY2010.[3]

Military service is associated with sleep loss and disruption, and its cause may be due to or exacerbated by the dynamic nature of military operations, sustained high operational tempo (OPTEMP) environments, frequent and rapid deployments, and occupational and family stressors.[5,104] A meta-analysis of longitudinal studies indicated that individuals with insomnia were twice as likely to develop depression compared to those without insomnia.[105] In a large prospective analysis of pre-deployment sleep symptoms in relation to mental health symptoms, it was found that pre-deployment insomnia symptoms were associated with higher odds of PTSD, depression, and anxiety post-deployment.[106]

In a 3-year follow-up of participants with insomnia from a large epidemiological study, those with more severe insomnia symptoms demonstrated greater persistence of insomnia symptoms relative to those with less severe insomnia symptoms at study inclusion.[37] In a prospective cohort study of middle-aged and elderly men and women in West Scotland, insomnia was more likely to become a chronic condition among participants who were older, female, or in a manual labor occupation.[38] Longitudinal

studies exploring persistent insomnia symptoms suggests a population prevalence ranging from 1-70%.[37–40] Few studies have evaluated the persistence or chronicity of sleep disturbance among military personnel or veterans; however, there is some evidence that sleep disturbances may persist after deployment conferring increased risk of chronic psychological distress such as depression, PTSD, and anxiety.[4,6]

A 2011 literature review of resilience to loss and potential trauma estimated that 35%-65% of military personnel experience little to no deleterious effects of events associated with deployment[107] This suggests that resiliency may be a key component as to why some service members develop persistent sleep disturbances. The aims of the current study are to: (1) Characterize the predominant trajectories of self-reported sleep quality over a 3-year period in active duty Army soldiers using Repeated Measures Latent Class Analysis (RMLCA) procedures; (2) Incorporate into a risk prediction model a broad range of potentially modifiable and non-modifiable (or potentially confounding) risk factors to include rank, deployment history, and psychosocial factors that may predict persistence of poor sleep quality; (3) Explore linkages between latent subgroup trajectories and various measures of military performance to include physical fitness scores, body composition, and weapon qualification. To our knowledge this is the first study to explore trajectories of self-reported sleep quality among active duty Army soldiers using data elements from the Global Assessment Tool 2.0.

3.3 Material and Methods

Study populations and procedures

The Global Assessment Tool 2.0 (GAT 2.0) is a required annual survey that is completed by all soldiers, and consists of 105 questions that assesses psychosocial

fitness in four dimensions to include emotional, social, family, and spiritual fitness.[108] In 2012, a physical dimension was added that measures sleep quality, dietary habits, physical fitness, and other lifestyle factors. In addition to the GAT 2.0, this study involved routinely collected data from multiple Department of Defense (DoD) and Army data sources to include the Defense Manpower Data Center (DMDC) and the Digital Training Management System (DTMS).

Eligible participants included soldiers who electronically consented to the use of their GAT 2.0 responses as of September 2013. We excluded soldiers who have not completed at least three GAT 2.0 surveys between the study inclusion dates of December 31, 2013 and August 31, 2017. No participants were excluded based on age, race, or gender. This study was approved by the institutional review boards at the U.S. Army Armament Research, Development and Engineer Center (ARDEC) and the University of South Carolina.

Out of 454,761 active duty soldiers who completed a GAT survey between December 1, 2013-August 31, 2017, 127,348 completed at least three surveys and had no missing socio-demographics (age, race, military status, and education) data.

Measures

Sleep. Sleep was assessed utilizing the two-item Pittsburgh Insomnia Rating Scale (PIRS-2) embedded in the GAT 2.0 survey. The PIRS-2 is a self-reported measure of perceived sleep quality, and is an efficient screening tool for the risk of insomnia.[1,109] The PIRS-2 asks about 1) overall sleep satisfaction, 2) how much a person was bothered by lack of energy due perceived poor sleep in the past 7 days. Each question has a score ranging from 0-3, and results in total scores ranging from 0-6, where higher scores

indicate increased risk for insomnia. It's Cronbach's α was 0.77 and had adequate test-retest and treatment-responsive characteristics. A cut-off score of 2 has a sensitivity of 96% sensitive and specificity of 86% for predicting insomnia.[1]

Demographics. Demographics such as age, gender (male or female), military status (junior enlisted, senior enlisted, junior officer/warrant, or senior officer/warrant) were collected from the GAT 2.0 survey; however, variables such as education level (no college vs some college), marital status (single/never married, married, or divorced/widowed/separated), and race (white, black, or other), were extracted from the DMDC data elements. Soldiers' with following military occupation specialties (MOS) were categorized as having a combat-arms occupation specialty: infantry, artillery specialists, air defense specialists, tank crew members, and special operations. All others were categorized as non-combat arms. In general, combat-arms occupations are considered to be more physically and psychologically demanding and require soldiers to frequently conduct tasks that require a combination of lifting, carrying, lowering, pulling, climbing, digging, walking, and running.[110]

GAT Dimensions: The psychosocial dimensions measured in the GAT 2.0 survey are a combination of multiple scales, some of which were designed specifically for the GAT and were originally identified by the World Health Organization (WHO) to include social, emotional, family, and spiritual fitness.[95] The social fitness dimension consists of subscales to evaluate work engagement, friendships, loneliness, and organizational trust. The emotional fitness dimension consists of subscales evaluating adaptability, coping, catastrophizing, depression, optimism, and affect. The family fitness consists of family satisfaction and military family support. The spiritual fitness dimension only consists of

the search for meaning scale. These measures and methods were developed by Seilgman et al. and have been evaluated previously.[108,111–113]

Dietary Habits. Dietary habits were assessed using the five-item Healthy Eating Score (HES-5). The HES-5 is based on the US Department of Agriculture's healthy eating index (HEI).[114] The HES-5 consists of five measures assessing the frequency of fruit, vegetables, whole grain, diary, and fish consumptions.[114] Scores range from 0-25, with higher scores representing healthier eating. HES-5 has been previously evaluated and has good internal consistency with a Cronbach α of 0.74.[115] For the purpose of this analysis HES-5 was dichotomized in way that soldiers with a sum score in the lowest quartile were recorded as having poor diet quality.[116]

Lifestyle Behaviors. Self-reported health behaviors such as alcohol use, tobacco use, physical activity, and work activity were assessed from the GAT 2.0 survey. Current tobacco use was derived from a question that asks participants about their use of the following tobacco products: cigarettes, cigars, smokeless tobacco, chew, and dipping in the past year. These responses were dichotomized based on regular use vs no use in the past year. Binge drinking was assessed with "Have you exceeded 5 alcoholic drinks on any single occasion during the past 3 months?". Participants who answered yes were classified as binge or heavy drinkers.[117] Participants self-reported their raw data score form their most recent Army Physical Fitness Test (APFT) scores. Body mass index (BMI) was derived from the self-reported height and weight, after excluding for biologically implausible values. Height was restricted to 48-84 inches (122-213 cm) and, weight was restricted to 75-500 pounds (34-227 kg).[3,118]

Measure of military performance. Various measures of military importance such at APFT scores, body composition metrics (BMI kg/m^2), pass/fail height weight standards; pass/fail body composition standards, and weapon (did not quality/Marksman/Sharpshooter/Expert) qualification were ascertained from the Digital Training Management System (DTMS), which provides Army leaders the ability to plan, resource, and manage unit and individual training at all levels. The APFT consists of a 2-min maximal effort pushup event, a 2-min maximal effort sit up event, and a 2-mile run performed for best time and are conducted in accordance with Army Field Manuel 7-22.[119]

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute. Inc., Cary NC.) Participants that were excluded from the analysis were compared with those who were included according to their characteristics at study inclusion using independent t-tests or Wilcoxon ranks sum test for continuous variables and chi-square tests for categorical variables. There were no significant differences between soldiers who were included in the study and those that were excluded on the bases of age, gender, race, education, rank, and PIRS-2 scores.

The RMCLA was performed using the *PROC TRAJ* procedure in SAS to identify subgroups with different trajectories of subject sleep quality over time.[120,121] RMLCA is used to estimate the overall probability of membership in each latent class, and can be used to explore associations between covariates and latent class membership.[122] This analysis assumes a mixture model to identify trajectories of unique subgroups that do not change over time. The identified latent subgroups have a specific intercept and slope that

were modeled rather than the trajectories of individual soldiers. Model fit was assessed primarily based on interpretability and parsimony of the model; however, bayesian information criterion (BIC), 95% confidence intervals, minimum latent subgroup size of ≥10% of the study population were also considered. Initially, a single class model was evaluated using a single quadratic trajectory. Since that model was statistically significant, the procedure was repeated with a two-class model. Next, the BIC for the two-class model was compared to the one-class model. If the quadratic function was not statistically significant for any trajectories, linear or cubic functions were sequentially fitted and the BICs were compared to the previous models. This iterative process was repeated with increasing numbers of trajectories until the best model was obtained.[123] Only participants who completed at least three GAT 2.0 surveys were included in the analysis (n=127,540; 443,731 observations). For the purposes of this analysis, time was coded as the amount of time in years between subsequent GAT 2.0 surveys from study inclusion.

Next, generalized estimating equation (GEE) models were estimated for repeated measures to identify characteristics that differed between the latent classes. This process was utilized to identify demographic, health-related, and military-related factors that differed between latent trajectory groups. For continuous variables, the relationship between latent groups were analyzed using an identify link and a normal distribution. For categorical variables this analysis was performed with a binary or multinomial distribution with a cumulative logit link with an unstructured or independent covariance matrix as appropriate. To select for potential covariates, bivariate relationships with each latent class were estimated, and variables with p-value ≤0.20 were selected for further

evaluation. A backwards covariate selection procedure was utilized, and variables that changed the effect estimate of latent class membership by ±10% or remained statistically significant with p-value ≤ 0.05 were included in the final model. A backwards selection procedure was utilized to develop the risk prediction model, and only variables with p-values ≤0.05 were retained in the final model.

Lastly, to further test the predicative capability of the variables included in the risk prediction model on predicting membership into the good or moderate trajectory groups versus the poor-sleep trajectory groups, an area under receiver operating characteristics (AUC ROC) curve analysis was performed using logistic regression. This analysis was conducted using variables at study baseline or study inclusion. In general, AUC ROC ≥0.9 is considered outstanding in ability to differentiate between predictive variables, 0.8 ≤AUC ROC < 0.9 is considered excellent; whereas, ≤0.7 AUC ROC <0.8 is considered adequate and AUC ROC below 0.7 is considered have poor predictive value.[124] For the purpose of this analysis members of the good and moderate sleep trajectories were condensed into one group.

3.4 Results

The study population was comprised of 127,348 soldiers for a total 444,615 repeated observations. Mean (SD) age of the sample was 29.7±7.7. The study population was primarily white (66%), male (85%), married (59%), have completed at least some college (69%). Additionally, 79% of the sample was enlisted and 23% were combat arms. At bassline, 67% of solider had PIRS-2 scores over 2 which meets the criteria for poor sleep. The mean (SD) follow-up time for the entire sample was 2.48±0.68 years;

2.51±0.68 years for the good-sleep trajectory group; 2.48±0.68 years moderate-sleep trajectory group; and 2.47±0.60 years for poor-sleep trajectory group. The study population characteristics are presented in Table 3.1

Latent Class Analysis. BIC improved with the addition of each latent class through 5 classes. The four (BIC =-785,234.1) and five (BIC =-784,417.5) class models were optimal according to BIC; however, the smallest classes for both models were below the a-priori selected 10% threshold. Therefore, the three (BIC =-788,763.9) class model was chosen. In addition, the four and five class models were not particularly informative as they did not provide adequate separation between trajectories thus we surmised that the three-class model was more specific for identifying groups of soldiers with persistent good and poor sleepers. The latent class trajectories for the four and five class models are presented in Figure A.1 and A.2 (Appendix A). The trajectory groups were characterized in a manner that is consistent with previous studies evaluating sleep quality using GAT 2.0 data.[104,115] The resulting latent trajectory groups were labeled as follows: 1) Good-Sleepers (n=18,962, 16%), Moderate-Sleepers (n=83,879, 62%), and Poor-Sleepers (n=24,507, 22%). The latent class trajectories for the three-class model are presented in Figure 3.2. As expected the good-sleep trajectory group had the lowest mean (SE) PIRS-2 scores (0.53±0.003) followed by the moderate (2.03±0.11) and poor (4.16±0.004) sleep groups. Summary fit statistics are presented in Table 3.2.

Comparison of latent classes. There were several noteworthy differences between the latent trajectory groups in terms of demographic, psychosocial, and military characteristics. In general, soldiers belonging to the poor-sleep trajectory group tended to be older (>30 years of age) (48%) compared to those in the good (46%) or moderate

(45%) sleep trajectory groups. Among soldiers in the poor-sleep trajectory group, a higher proportion were female (19%), black (27%), married (60%), and have not attended college (76%) compared to the good or moderate sleep trajectory groups. Additionally, poor-sleepers were more likely to be enlisted (86%) and have non-combat arms (78.4%) military occupations; whereas, good-sleepers tended to be officers or warrant officers. Among the GAT 2.0 psychosocial dimensions, members of the poor-sleep trajectory groups had significantly lower levels of emotional, social, family, and spiritual fitness scores. A higher proportion of soldiers in the poor-sleep trajectory group also had poorer health behavior characteristics in terms of diet, alcohol use, tobacco use, and physical activity. Results are presented in Tables 3.3 and 3.4.

Predictors of latent class membership. Results of multivariable GEE analysis with the latent trajectory group membership as the outcome of interest are presented in Table 3.4. Soldiers who were older, female, non-white, and of Hispanic descent were less likely to be members of good or moderate trajectory groups. Additionally, being senior enlisted, warrant officer, or officer were more likely to be members of the good vs moderate or poor trajectory groups compared to junior enlisted soldiers. Soldiers with a combat military occupation were more likely to be members of a better sleep trajectory groups compared to non-combat military occupations. Soldiers with increased emotional and family fitness score also were more likely to be members of the good and moderate sleep trajectory groups. Other variables that were significantly associated with being a member of the good vs moderate or poor sleep trajectory groups included current tobacco use and education (some college vs no college). Lastly, those who binge drink, have a poor diet, or low physical activity (less than 3 times per week) were less likely to be

members of the good or moderate sleep trajectory groups (Table 3.4). Results from the AUC ROC analyses are presented in Figure 3.3. Only depression and total psychosocial fitness scores demonstrated adequate ability to different between a member of good/moderate and poor sleep trajectory groups.

Outcomes of military importance. Results from the multivariable GEE analysis are presented in Table 3.5 and 3.6. Analyses exploring the relationship between latent trajectory group membership and the various outcomes of military importance included 127,348 soldiers; 264,836 observations for body composition metrics, 454,985 observations for APFT measures, and 287,450 observations for weapon qualification measures. Membership in the good and moderate sleep trajectory group was associated with increased odds of passing the APFT, height-weight, body composition, and weapon qualification standards compared to members of the poor-trajectory group. Members of the good (OR=1.19, 95% CI 1.14-1.23) and moderate (OR = 1.22, 95% CI 1.18-1.26) trajectory groups had higher odds having a normal BMI. Additionally, the good (OR=0.37, 95% CI 0.36-0.39) and moderate (OR=0.60, 95% CI 0.58-0.61) sleepers also had lower odds of self-reporting a musculoskeletal injury during the study period.

3.5 Discussion

This prospective analysis of active US Army soldiers revealed three different latent trajectory subgroups that consisted of soldiers who were alike in terms of their longitudinal trajectories of self-reported sleep quality. Most of the sample was classified as either moderate (62%) or poor (23%) sleepers. In general, the soldiers with poorer sleep trajectories tended to be female, non-white, enlisted, and have non-combat related

military occupation. Soldiers with consistently better sleep quality had better body composition metrics, Army physical fitness scores, and were more likely to meet weapon qualification standards. A central finding from this study is that the psychosocial fitness constructs defining higher resiliency, characterized as emotional, social, family, and spiritual fitness, were independently associated with better sleep quality trajectories. Unexpectedly, increased rank and having a combat military occupation were associated with better sleep quality trajectories. Social desirability may be an explanation as to why higher rank and combat occupations were more likely to be members of better sleep trajectory groups. In a study consisting of 216 Swedish military officers, results suggested that officers tend to answer personality tests in a socially desirable manner in order to "look good."[125] Additionally, previous work has demonstrated that military personnel fear seeking mental health services to avoid perceived negative consequences to their careers, and avoid the appearance of weakness by their superiors and coworkers.[126,127] Lastly, a 2009 Mental Health Advisory report found that approximately 34% of soldiers serving in Afghanistan believed that they would be treated differently by their units if they pursued mental health care, and that over 50% believed they would be perceived as weak.[128]

These results are consistent with a few other longitudinal studies that have reported the persistence of diagnosed insomnia and insomnia symptoms to be; 74% for at least one year with rates over 40% for periods extending 3-20 years.[38,129–131] Gender, racial, ethnic, and age differences were also consistent with previous work.[132,133] The majority of previous studies evaluating the longitudinal patterns of sleep disturbance over time have used sleep duration as the primary measure.[6,42,134,135] The current analysis

used the PIRS-2 score as the outcome measure, and self-reported sleep duration was strongly associated with group membership. Specifically, members of the poor-sleep group had higher prevalence of short sleep duration (<6 hours) during the work week compared to good or moderate trajectory groups. Contrary to previous studies, sleep quality trajectories remained fairly constant in the present study whereas others have reported worsening sleep quality trajectories over time. [42,136]

Strengths of this study include a nationally representative sample of US Army soldiers, the longitudinal design encompassing 3 years, and an established/validated measure of subjective sleep quality, as well as the availability of multiple measures of psychosocial fitness and modifiable health behaviors. Additionally, the use of Person-Event Data Environment allows for the linkage to various other DoD data sources allowing subsequent longitudinal analyses. There are few noteworthy limitations of this analysis. Despite the longitudinal nature of the study, the data were collected and evaluated in a cross-sectional manner, thus differences in demographic, military characteristics, and health-behaviors between the latent groups are not necessarily suggestive of a causal relationship. We also cannot exclude the possibility of reverse causality. For example, while the psychosocial fitness scores were predictors of latent trajectory membership, we were not able to determine if resiliency was determinant or consequence of persistently better sleep quality. However, the mean values for each psychosocial fitness score remained relatively constant over the course of the study (Table 3.7). Also, since sleep was measured by self-report and not objectively, some misclassification of true sleep quality is a possibility. Previous work has found that self-reported sleep data tends to overestimate sleep duration; however, since trajectories were

stable over time, any overestimation is expected to be stable.[42,137] Self-reported sleep measures also are subject to recall and social desirability biases.[138] There are a few noteworthy reasons as to why this may be the case: 1) A brief questionnaire format may not be suitable to capture the complex nature of sleep; 2) Participants may unknowingly round or adjust single point estimates of sleep based on factors such as seasons; 3) and subjective questionnaires may be measuring underlying personality traits and cognitive processes vs subjective sleep quality itself.[138] In addition, the PIRS-2 questionnaire consists of only two items; whereas, the original PIRS questionnaire consists of 60 questions and the Pittsburgh Sleep Quality Index consists of 20 questions. Therefore, the PIRS-2 may not adequately characterize the various subtypes of sleep disorders and disturbances. However, despite this limitation the PIRS-2 questionnaire may be more appropriate for large-scale epidemiological studies; whereas, the 60-item version is more suitable psychiatric purposes.[1] While self-reported sleep measures are cost-effective when conducting large-scale epidemiological studies they are subject to reporting biases in contrast to objective measures of sleep such at wrist-actigraphy and polysomnography. Lastly, this study may not be generalizable to civilian population or the other service components (eg. Navy or Airforce). The other service components confer different operational and cultural stressors, mission focuses, and deployment characteristics.

The deleterious health effects of poor sleep quality have received ever increasing attention as public health problems, to the extent that it has become a core component of the U.S. Army Surgeon Generals Performance Triad of improving nutrition, physical activity, and sleep in soldiers. In previous military research, poor sleep has been

associated with increased risk of depression, PTSD, suicide, and other mental health disorders.[7,139,140]

In conclusion, this study is the first to our knowledge to evaluate the longitudinal trajectories of subjective sleep quality using repeated measures latent class analysis procedures, in a national sample of active duty Army personnel. We were able to identify demographic, psychosocial, and health behavior characteristics that predict persistently poor sleep quality. Soldiers with persistent poor sleep quality were more likely to be female, have a non-combat military occupation, have poor diet quality, and were less likely to meet physical fitness, body composition, and weapon qualification standards. Lastly, soldiers in the poorer sleep trajectory groups had lower levels of resiliency across all psychosocial fitness dimension measured by the GAT 2.0. It is widely accepted that the demands of military service, especially in combat or deployed environments restricts a soldier's opportunity for adequate sleep. To date there is no evidence-based practices or interventions that prevent sleep disorders in military or civilian populations with the exception of obstructive sleep apnea.[141] Therefore, segments of this and similar populations such as veterans, police, firefighters, or others may benefit from initiatives that target characteristics contributing to persistent poor sleep. Future work should focus on whether persistently poor sleep is independently associated with increased risks for adverse health outcomes, cognitive function, mortality, and long-term disability versus the traditional notion that poor sleep is a consequence of an underlying physical or mental health problem.

Table 3.1 Demographic characteristics at study inclusion (n=127,348, 443,731 observations)

Characteristics	All Participants
	Mean ± SD or n (%)
Age Groups	
17-29 years	69,421 (54.5)
30-40 years	44,719 (35.1)
>40 years	13,208 (10.4)
Diet[1]	
Healthy	18,743 (14.7)
Unhealthy	108,605 (85.3)
Gender	
Male	108,429 (85.1)
Female	18,919 (14.9)
Race	
White	84,118 (66.1)
Black/African American	28,878 (22.7)
Other	14,352 (11.3)
Ethnicity	
Non-Hispanic Latino	110,671 (86.9)
Hispanic/Latino	16,667 (13.1)
Marital Status	
Single/Never Married	44,957 (35.3)
Married	75,664 (59.4)
Divorced/Widowed/Separated	6,715 (5.3)

Table 3.1 Demographic characteristics at study inclusion (n=127,348, 443,731 observations) (continued)

Characteristics	All Participants
	Mean ± SD or n (%)
Education	
No College	88,202 (69.3)
Some college or more	39,146 (30.7)
Rank	
Junior Enlisted	48,741 (38.5)
Senior Enlisted	51,869 (40.9)
Junior Officer/Warrant	18,218 (14.4)
Senior Officer/Warrant	7,875 (6.2)
MOS Category	
Combat Arms[3]	28,778 (23.2)
Non-Combat Arms	95,036 (76.8)
Alcohol use	
Non-Binge Drinker	114,056 (89.6)
Binge Drinker	13,292 (10.4)
Vigorous physical activity at least 3 times per week	
Yes	106,180 (83.4)
No	21,168 (16.6)
Work activity	
Moderate to high activity	84,007 (66.0)
Low to sedentary activity	43,341 (34.0)
Current tobacco use	
Yes	21,637 (17.0)
No	105,711 (83.0)

Table 3.1 Demographic characteristics at study inclusion (n=127,348, 443,731 observations) (continued)

Characteristics	All Participants
	Mean ± SD or n (%)
Sleep medication	
Yes	8,159 (6.4)
No	119,189 (93.59)
Sleep duration during work/duty week	
<6 hours	35,727 (28.1)
6-7 hours	81,472 (64.0)
≥8hours	10,149 (8.0)
Sleep duration during the weekend/days off	
<6 hours	11,569 ± 9.1
6-7 hours	54,381 ± 42.7
≥8hours	61,398 ± 4 8.2
Age, years	29.7 ± 7.7
APFT[2]	259.9 ±3 4.6
BMI (kg/m^2)[2]	26.4 ± 3.6
Depression	15.1 ± 6 .5
Emotional Fitness[4]	4.1 ± 0.5
Social Fitness[4]	4.1 ± 0.6
Family Fitness[4]	4.3 ± 0.7
Spiritual Fitness[4]	4.3 ± 0.7
Number of days deployed (OEF/OIF/OND)	351.7 ± 404.6
Percentages not totaling 100% are due to rounding. [1]Healthy diet is defined as a total Healthy Eating Score-5 ≥ 20 out of 25. [2]Varibles are self-reported. [3]11, 13,14, and 18 series Military Occupational Specialties are considered combat arms. [4]Higher scores indicated increased levels of psychosocial fitness. Abbreviations: BMI = Body Mass Index; APFT = Army Physical Fitness Test; SD = Standard Deviation; MOS= Military Occupational Specialty; OEF=Operation Enduring Freedom; OIF=Operation Iraq Freedom; OND=Operation New Dawn.	

Table 3.2 Fit statistics for latent class models

Number of Classes	BIC	AIC	2ΔBIC	Smallest sample size (%)[a]
1	-838833.3	-838811.3	--	--
2	-801791.2	-801747.2	74084.2	62, 496 (49.8%)
3	**-788763.9**	**-788697.9**	**26054.6**	**20,559 (16.1%)**
4	-785234.1	-785148.6	7059.6	8,303 (6.5%)
5	-784417.5	-784405.1	1633.2	4,400 (3.55%)

Abbreviations: df = degrees of freedom; AIC = Akaike Information Criterion; BIC= Bayesian Information Criterion; 2ΔBIC = $BIC_{complex} - BIC_{Null,}$ the difference in BIC between the two models is a measure of the evidence against the null. Values >10 provide convincing evidence against the null. [a]The number and percentage of active duty soldiers in the smallest class.
Bold indicates the selected model.

Table 3.3 Characteristics of latent groups: 2-item Pittsburgh Insomnia Rating Scale (n= 127,348, 443,731 observations)

Variables	2-item Pittsburgh Insomnia Rating Scale			p-value[2]
	Good (n=18,959)	Moderate (n=83,864)	Poor (n=24,499)	
	(0.53±0.003)[1]	(2.03±0.11)[1]	(4.16±0.004)[1]	
	%	%	%	
Age Groups				
17-29 years	54.2*	55.4*	51.7	<0.01
30-40 years	34.2*	34.6*	37.5	
>40 years	11.6*	10.0*	10.8	
Gender				
Male	90.2	85.2*	81.0	<0.01
Female	9.8	14.8*	19.0	
Race				
White	72.2*	66.2*	60.9	<0.01
Black/African American	17.7*	22.5*	27.1	
Other	10.1*	11.3*	12.0	
Ethnicity				
Non-Hispanic Latino	87.2	87.1*	85.9	<0.01
Hispanic/Latino	12.8	12.9*	14.1	
Marital Status				
Never Married/Single	35.0*	36.1*	32.9	<0.01
Married	60.8*	58.9*	60.3	
Divorced/Widowed/Separated	4.1*	5.1*	6.9	

Table 3.3 Characteristics of latent groups: 2-item Pittsburgh Insomnia Rating Scale (n= 127,348, 443,731 observations) (continued)

Variables	2-item Pittsburgh Insomnia Rating Scale			p-value[2]
	Good (n=18,959)	Moderate (n=83,864)	Poor (n=24,499)	
	(0.53±0.003)[1]	(2.03±0.11)[1]	(4.16±0.004)[1]	
	%	%	%	
Education				
No College	64.6*	68.5*	75.5	<0.01
Some college or more	35.4*	31.5*	24.5	
Rank				
Junior Enlisted	37.2*	37.4*	39.2	<0.01
Senior Enlisted	37.3*	40.0*	46.8	
Junior Officer/Warrant	16.8*	15.2*	9.9	
Senior Officer/Warrant	8.2*	6.4*	4.1	
MOS Category				
Combat Arms	25.4*	23.2*	21.6	<0.01
Non-Combat Arms	74.6*	76.8*	78.4	
Alcohol use				
Non-Binge Drinker	93.3*	89.5*	86.9	<0.01
Binge Drinker	6.7*	10.5*	13.2	
Vigorous physical activity at least 3 times per week				
Yes	88.4*	83.6*	78.7	<0.01
No	11.6*	16.4*	21.3	
Diet				
Healthy	26.3*	13.7*	9.2	<0.01
Unhealthy	73.7*	86.3*	90.8	

Table 3.3 Characteristics of latent groups: 2-item Pittsburgh Insomnia Rating Scale (n= 127,348, 443,731 observations) (continued)

Variables	2-item Pittsburgh Insomnia Rating Scale			p-value[2]
	Good (n=18,959)	Moderate (n=83,864)	Poor (n=24,499)	
	(0.53±0.003)[1]	(2.03±0.11)[1]	(4.16±0.004)[1]	
	%	%	%	
Current tobacco use				
Yes	14.1	16.5*	21.1	<0.01
No	85.9	83.5*	79.0	
Work activity				
Moderate to high activity	68.2	66.0*	64.3	<0.01
Low to sedentary activity	31.8	34.1*	35.7	
Sleep medication				
Yes	2.5*	5.3*	13.2	<0.01
No	97.6*	94.7*	86.8	
Sleep duration during work/duty week				
<6 hours	8.9*	24.9*	53.8	<0.01
6-7 hours	70.7*	68.5*	43.4	
≥8hours	20.4*	6.7*	2.8	
Sleep duration during the weekend/days off				
<6 hours	3.1*	7.4*	19.4	<0.01
6-7 hours	35.1*	43.7*	45.1	
≥8hours	61.8*	48.9*	35.5	

Higher scores of emotional, social, and family fitness indicate higher levels of resilience in each dimension. Each predictor was evaluated in separate bivariate model. Healthy diet is defined as a total Healthy Eating Score – 5 ≥ 20 out of 25.
[1]Mean±SE for PIRS-2. [2]Overall F-test for p-value for variable of interest. Abbreviations: SE = Standard Error. *p-value ≤0.05 versus poor-sleep trajectory group.

Table 3.3 Characteristics of latent groups: 2-item Pittsburgh Insomnia Rating Scale (n= 127,348, 443,731 observations) (continued)

Variables	2-item Pittsburgh Insomnia Rating Scale			p-value[2]
	Good (n=18,959)	Moderate (n=83,864)	Poor (n=24,499)	
	(0.53±0.003)[1]	(2.03±0.11)[1]	(4.16±0.004)[1]	
	Mean ± SE	Mean ± SE	Mean ± SE	
Age, years	31.2±0.06	30.8±0.03*	31.3±0.05	<0.01
BMI (kg/m^2)	26.5±0.18	26.8±0.06	27±0.20	0.17
Depression	11.3±0.02*	15.3±0.41*	22.0±0.04	<0.01
Total Fitness	4.52±0.03*	4.16±0.02*	3.70±0.06	<0.01
Emotional Fitness	4.38±0.05*	4.03±0.03*	3.74±0.06	<0.01
Social Fitness	4.45±0.01*	4.08±0.005*	3.67±0.02	<0.01
Family Fitness	4.59±0.003*	4.26±0.001*	3.87±0.004	<0.01
Spiritual Fitness	4.45±0.12*	4.36±0.05*	3.83±0.14	<0.01
Number days deployed (OEF/OIF/OND)	332.4±2.86*	346.2±1.39*	383.0±2.65	<0.01

Abbreviations: OR = Odds Ratio; CI = Confidence Interval; SE = Standard Error; BMI = Body Mass Index (self-reported); OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OND = Operation New Dawn. Higher scores of total, emotional, social, and family fitness indicate higher levels of resilience in each dimension. Each predictor was evaluated in separate bivariate models. [1]Mean±SE for PIRS-2. [2]Overall F-test p-value for variable of interest. *p-value ≤0.05 versus poor-sleep group.

Table 3.4 Multivariable predictors of good sleep trajectory membership in active duty Army soldiers.

Variables	OR (95% CI)	p-value
Age Groups		
17-29 years	Ref	<0.01
30-40 years	0.92 (0.89-0.95)	
>40 years	0.85 (0.80-0.89)	
Gender		
Male	Ref	<0.01
Female	0.66 (0.64-0.68)	
Race		
White	Ref	<0.01
Black/African American	0.71 (0.69-0.73)	
Other	0.82 (0.79-0.86)	
Ethnicity		
Non-Hispanic Latino	1.16 (1.12-1.21)	<0.01
Hispanic/Latino	Ref	
Marital Status		
Never Married/Single	1.14 (1.10-1.18)	<0.01
Married	Ref	
Divorced/Widowed/Separated	0.96 (0.91-1.02)	
Education		
No College	Ref	<0.01
Some college or more	1.06 (1.02-1.10)	

Table 3.4 Multivariable predictors of good-sleep trajectory membership in active duty Army soldiers. (continued)

Variables	OR (95% CI)	p-value
Rank		
Junior Enlisted	Ref	<0.01
Senior Enlisted	1.04 (1.01-1.08)	
Junior Officer/Warrant	1.17 (1.12-1.23)	
Senior Officer/Warrant	1.37 (1.28-1.46)	
MOS Category		
Combat Arms	Ref	<0.01
Non-Combat Arms	0.95 (0.93-0.99)	
Alcohol use		
Non-Binge Drinker	Ref	<0.01
Binge Drinker	0.93 (0.89-0.97)	
Vigorous physical activity at least 3 times per week		
Yes	Ref	<0.01
No	0.90 (0.87-0.93)	
Diet		
Healthy	Ref	<0.01
Unhealthy	0.63 (0.61-0.65)	
Current tobacco use		
Yes	Ref	<0.01
No	1.07 (1.03-1.11)	
Sleep medication		
Yes	Ref	<0.01
No	1.61 (1.53-1.71)	
Depression	0.90 (0.90-0.91)	<0.01
Total Fitness	2.01 (1.97-2.09)	<0.01

Table 3.4 Multivariable predictors of good-sleep trajectory in active duty Army soldiers. (continued)

Variables	OR (95% CI)	p-value
OEF/OIF Deployment		
Yes	Ref	<0.01
No	1.06 (1.02-1.10)	
Abbreviations: OR = Odds Ratio; CI = Confidence Interval. Higher scores of total fitness indicate higher levels of overall resilience in each dimension. Healthy diet is defined as a total Healthy Eating Score-5 ≥ 20 out of 25.		

Table 3.5 Association between latent class membership and military characteristics (n= 127,348)

Variables	Latent Class Membership			p-value
	Good (n=18,959)	Moderate (n=83,864)	Poor (n=24,499)	
	(0.53±0.003)[1]	(2.03±0.11)[1]	(4.16±0.004)[1]	
	Mean ± SE	Mean ± SE	Mean ± SE	
Weight (Kg)	84.9±2.00*	83.1±1.48*	79.5±1.92	0.03
BMI (kg/m^2)	28.9±0.73*	28.1±0.54*	26.6±0.69	<0.01
APFT[c]	256.5±0.52*	248.1±0.43*	235.4±0.53	<0.01
Models adjusted for time education, marital status, race, gender, rank, tobacco use, and MOS category. Abbreviations: SE = Standard Error; APFT = Army Physical Fitness Test; BMI = Body Mass Index (kg/m^2); kg = Kilograms. [1]Mean±SE for PIRS-2. [2]Overall F-test for p-value for variable of interest. *p-value ≤0.05 versus poor-sleep group.				

Table 3.6 Association between latent class membership and military characteristics (n= 127,348)

Variables	OR (95% CI)	p-value
Musculoskeletal Injury		
Good Sleeper	0.37 (0.36-0.39)	<0.01
Moderate Sleeper	0.60 (0.58-0.61)	
Poor Sleeper	Ref	
APFT Pass		
Good Sleeper	1.87 (1.77-1.99)	<0.01
Moderate Sleeper	1.36 (1.31-1.42)	
Poor Sleeper	Ref	
Height Weight		
Good Sleeper	1.41 (1.35-1.47)	<0.01
Moderate Sleeper	1.21 (1.17-1.25)	
Poor Sleeper	Ref	
Body Composition		
Good Sleeper	1.94 (1.78-2.11)	<0.01
Moderate Sleeper	1.46 (1.38-1.54)	
Poor Sleeper	Ref	
Weapon Qualification		
Good Sleeper	1.08 (1.05-1.12)	<0.01
Moderate Sleeper	1.03 (1.00-1.05)	
Poor Sleeper	Ref	
Models adjusted for time, education, marital status, race, gender, rank, tobacco use, and MOS category. Abbreviations: OR = Odds Ratio; CI = Confidence Interval; APFT = Army Physical Fitness Test; MOS = Military Occupational Specialty; Ref = Reference.		

Table 3.7 Adjusted mean values of psychosocial fitness scores stratified by year of Global Assessment Tool 2.0 completion

Fitness Scores	Latent Class Membership	Follow-up time in years			
		2014	2015	2016	2017
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Total	Good	4.38±0.007	4.38±0.02	4.28±0.03	5.42±0.21
	Moderate	4.12±0.006	4.12±0.02	4.05±0.05	4.99±0.18
	Poor	3.83±0.007	3.82±0.02	3.77±0.06	4.33±0.2
Emotional	Good	4.25±0.007	4.23±0.02	4.09±0.05	4.54±0.21
	Moderate	3.98±0.006	3.96±0.02	3.82±0.05	4.20±0.18
	Poor	3.71±0.007	3.68±0.02	3.57±0.06	3.72±0.18
Social	Good	4.37±0.008	4.36±0.02	4.28±0.06	5.38±0.22
	Moderate	4.09±0.007	4.07±0.02	4.02±0.06	5.07±0.18
	Poor	3.76±0.008	3.77±0.02	3.68±0.06	4.40±0.19
Family	Good	4.41±0.01	4.14±0.02	4.43±0.08	6.12±0.29
	Moderate	4.16±0.01	4.14±0.02	4.20±0.07	5.53±0.24
	Poor	3.86±0.01	3.84±0.02	3.94±0.08	4.97±0.21
Spiritual	Good	4.58±0.01	4.58±0.02	4.44±0.08	5.26±0.32
	Moderate	4.32±0.01	4.33±0.02	4.22±0.08	4.83±0.27
	Poor	4.05±0.01	4.05±0.02	3.95±0.08	4.16±0.31

Models adjusted for year, age, education, rank, MOS, alcohol, physical activity, tobacco use, sleep medication, and diet.
Higher scores of the total, emotional, social, family, and spiritual fitness indicates higher levels of resilience in each dimension.
Abbreviations: SD = Standard Deviation; MOS = Military Occupation Specialty.

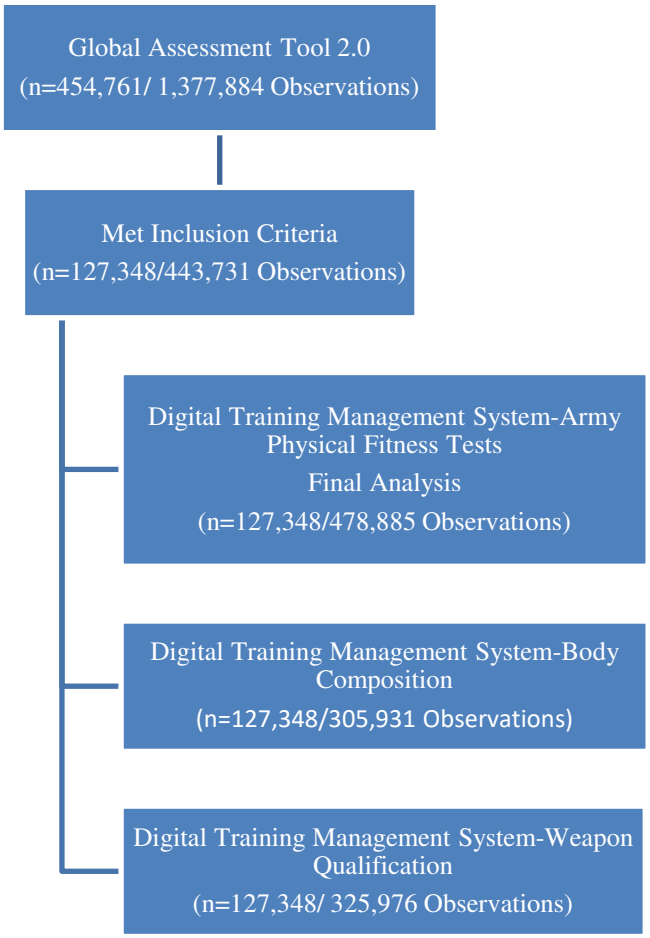


Figure 3.1 Study flow for manuscript 1. Inclusion criteria for this study are active duty Army soldiers who completed at least 3 Global Assessment Tool 2.0 (GAT 2.0) surveys between December 31, 2013 and August 31, 2017 and had no missing data for the 2-item Pittsburgh Insomnia Rating Scale (PIRS-2), race, and education.

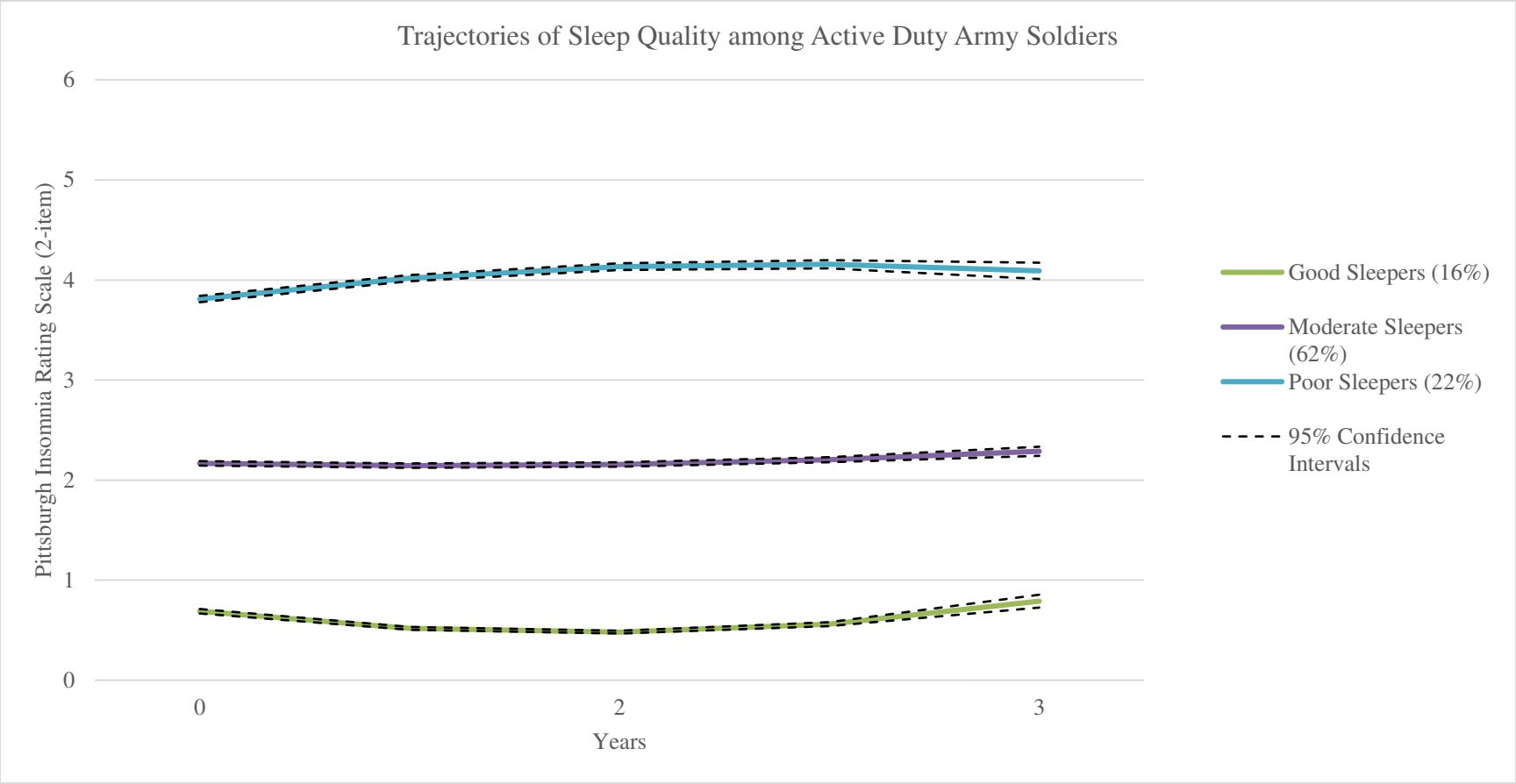


Figure 3.2 Latent group trajectories (3-class Model) for PIRS-2 sleep measures over 3 years obtained with repeated measures latent class analysis (n=127,348). Only participants who have completed 3 GAT 2.0 Surveys from December 31, 2013 – August 31, 2017 were included. A cut-off score of 2 was 96% sensitive and 86% specific for determining the presence of insomnia.[109]

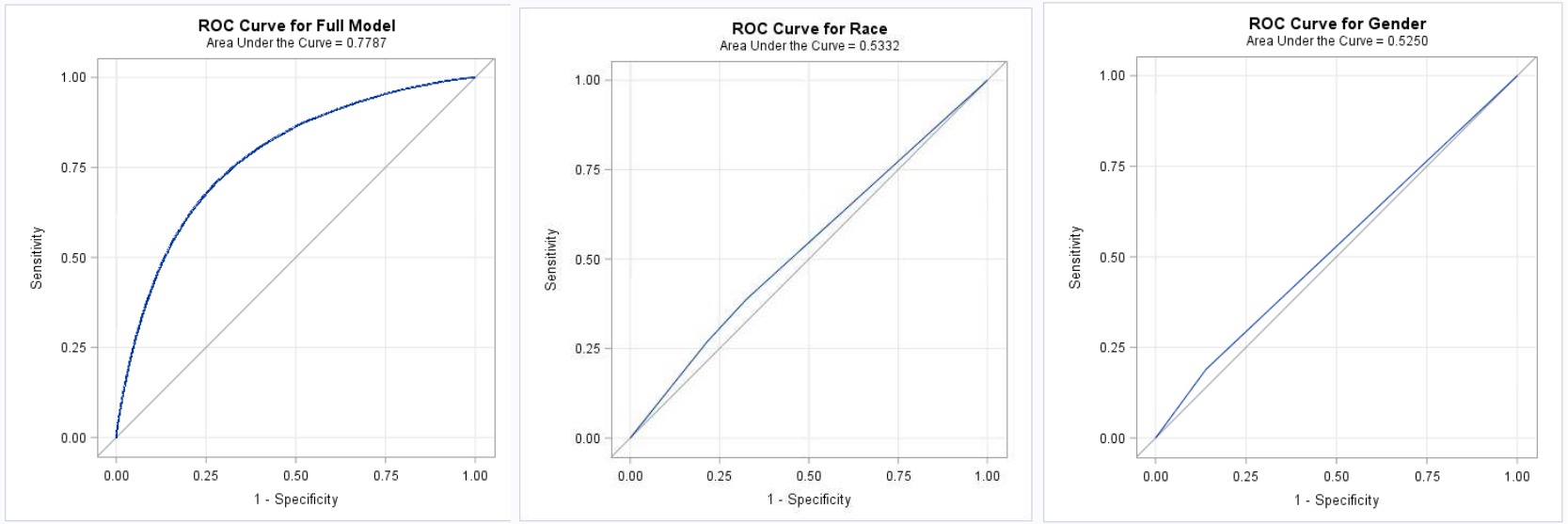


Figure 3.3 Receiver operating characteristic curves for membership to poor-sleep trajectory group. Full model area under the curve = 0.78; 95% confidence interval: 0.78-0.78; Race area under the curve = 0.53; 95% confidence interval: 0.53-0.54; Gender area under the curve = 0.53; 95% confidence interval: 0.52-0.53.

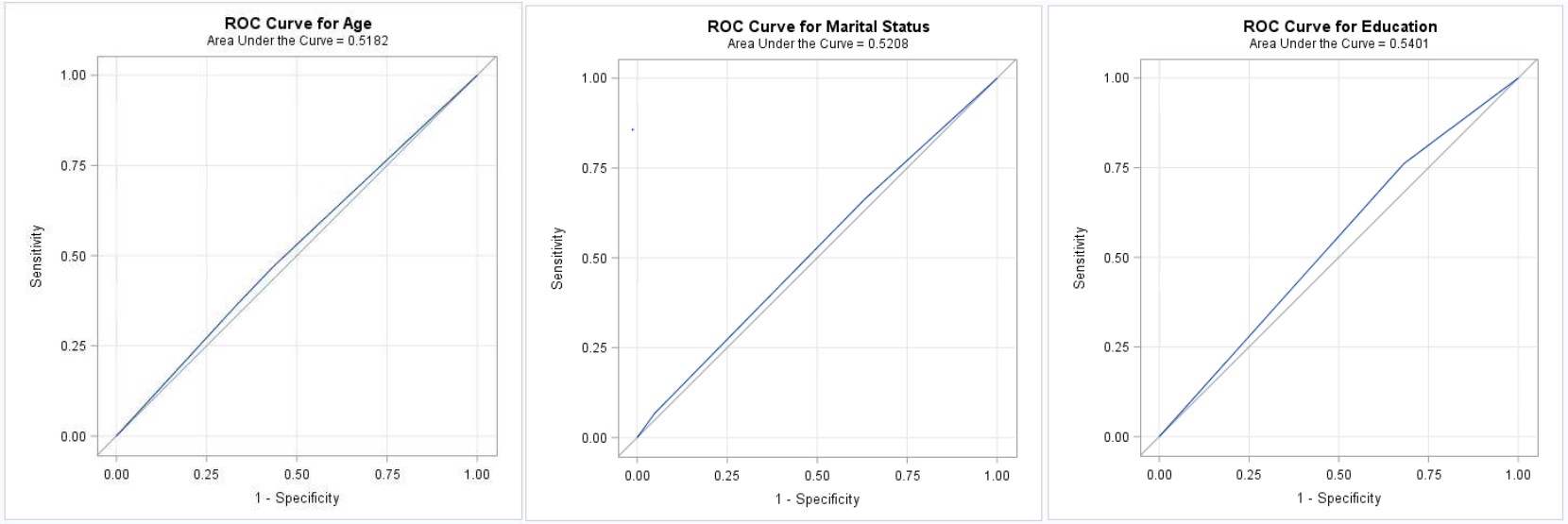
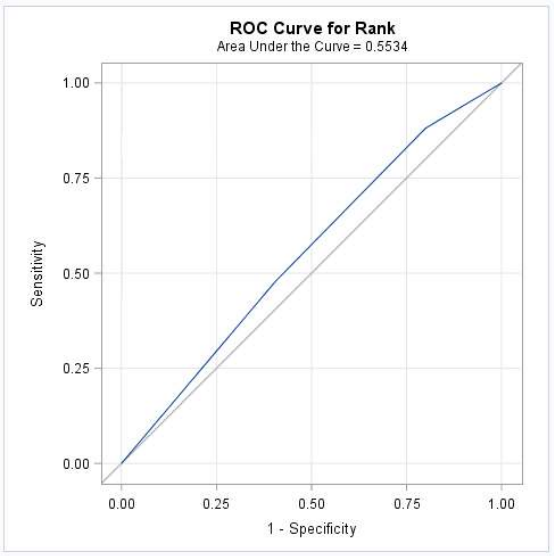
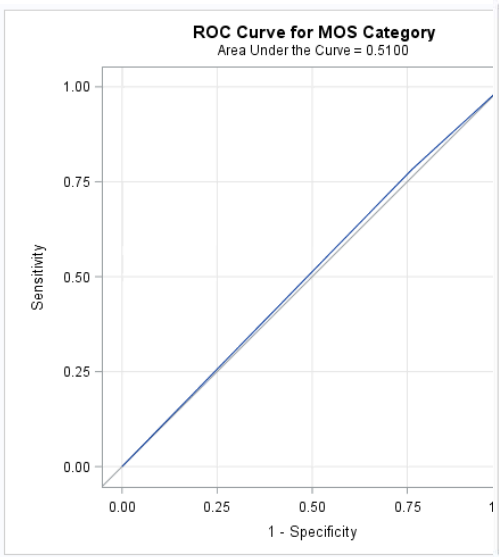


Figure 3.3 Receiver operating characteristic curves for membership to poor-sleep trajectory group (continued). Age area under the curve =0.52; 95% confidence interval:0.51-0.52; Marital status area under the curve = 0.52; 95% confidence interval: 0.52-0.52; Education area under the curve = 0.54; 95% confidence interval: 0.54-0.54.





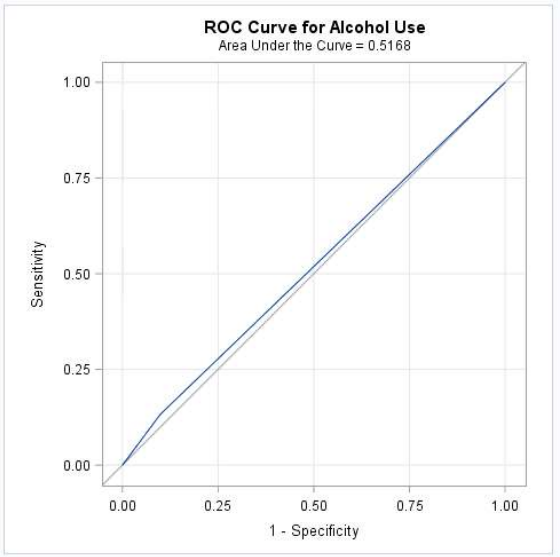


Figure 3.3 Receiver operating characteristic curves for membership to poor-sleep trajectory group (continued). Rank area under the curve = 0.55; 95% confidence interval:0.54-0.56; MOS category area under the curve = 0.51; 95% confidence interval: 0.51-0.51; Alcohol use area under the curve =0.52; 95% confidence interval: 0.51-0.52.

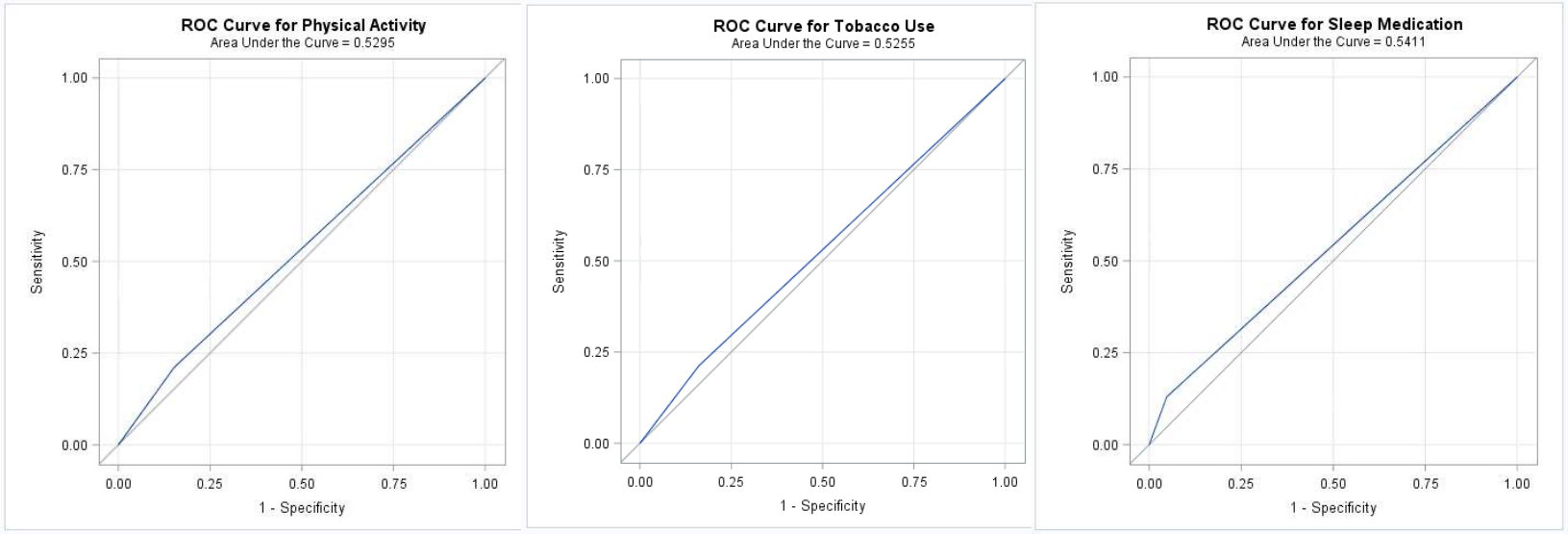


Figure 3.3 Receiver operating characteristic curves for membership to poor-sleep trajectory group (continued). Physical activity area under the curve = 0.53; 95% confidence interval: 0.53-0.53; Tobacco use area under the curve =0.53; 95% confidence interval: 0.52-0.53; Sleep medication area under the curve = 0.54; 95% confidence interval: 0.54-0.54.

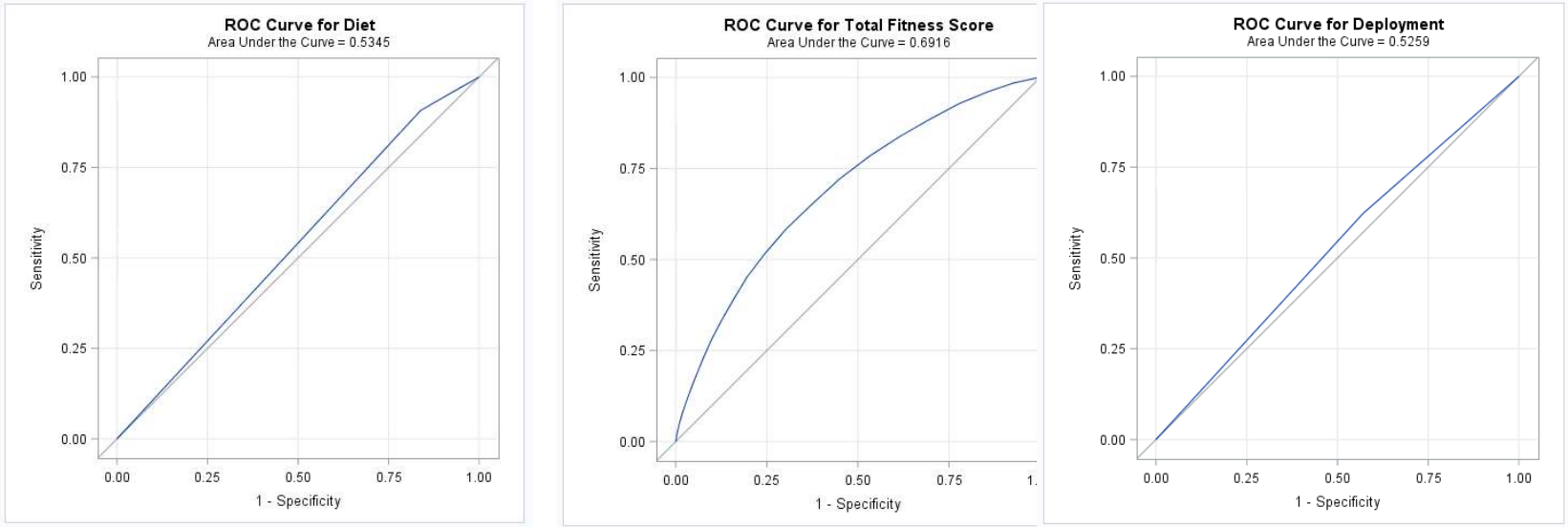


Figure 3.3 Receiver operating characteristic curves for membership to poor-sleep trajectory group (continued). Diet area under the curve = 0.53; 95% confidence interval: 0.53-0.54; Total fitness score area under the curve = 0.69; 95% confidence interval: 0.69-0.67; Deployment area under the curve = 0.53; 95% confidence interval: 0.53-0.53.

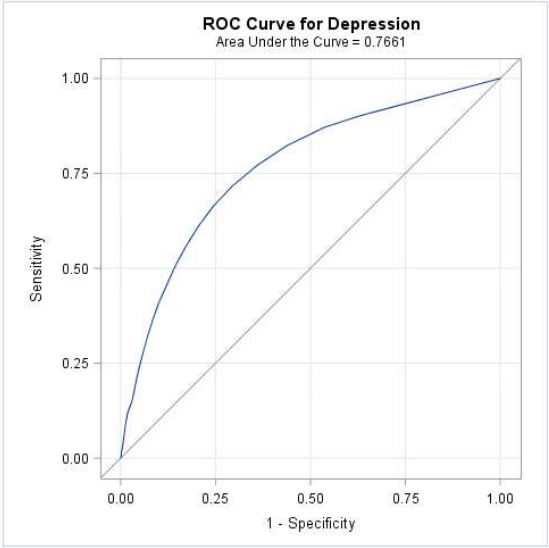


Figure 3.3 Receiver operating characteristic curves for membership to poor-sleep trajectory group (continued). Depression area under the curve = 0.77; 95% confidence interval: 0.76-0.77

CHAPTER 4

SHIFTWORK ADAPTATION AMONG POLICE OFFICERS: THE BCOPS STUDY[2]

[2] Nevels, T., J.B. Burch, M. Wirth, A. Mclain, JP. Ginsberg, P. Allison, D. Fekedulegn, J. Violanti. To be submitted to *Chronobiology International or Sleep*.

4.1 Abstract

Introduction. Policing routinely requires the officer to sleep at inappropriate times leading to the rearrangement of wake and sleep times. These changes can lead to disruption of circadian rhythms which may lead to dysregulation of various physiological processes and increased psychological disturbances. Despite the obvious health effects of shiftwork, there are individuals who appear to tolerate shiftwork better than others. **Objectives.** To identify the predominant subgroups that characterize adaptation to shiftwork among 242 police officers who are participants of the Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) study. Additionally, we evaluated a broad range of potentially modifiable, as well as non-modifiable, risk factors that may predict adaptation to shiftwork. Lastly, this study examined multiple biomarkers to include inflammatory, heart rate variability (HRV) indices, and cardiometabolic risk characteristics among the resultant latent classes. **Methods.** The study consisted of 242 police officers from the BCOPS study. A latent class analysis was used to identify subgroups using a-priori indicator variables and a latent class variable selection procedure to identify the most parsimonious model. Resultant latent classes were compared using generalized linear models or chi-square tests to identify characteristics that differed among the latent subgroups. **Results.** The 2-class model was determined to be optimal. The selected 2-class model included a class of individuals (shiftwork maladapted, n = 73) who had moderate-high probability of have self-reported sleep disturbances ≥2 times per week in last 30 days, sleep latency > 30min in the last 30 days, high lack of support, high perceived stress, and symptoms of fatigue; whereas, the other class (shiftwork adapted, n= 169) had relatively low probability of those behaviors. With

exception of Leptin, there were no differences in inflammatory markers, HRV indices, or cardiometabolic risk factors. **Discussion.** This study identified factors that may contribute to maladaptation to shiftwork. Modifiable factors such as stress, fatigue, sleep disruption, and poor family interactions can be targeted for more effective shiftwork adaptation programs among police officers.

4.2 Introduction

Policing is widely considered to be one of the most stressful occupations and is associated with increased morbidity and mortality when compared to the general population.[142–144] Prior research has shown that police work is associated with a higher chronic disease burden to include certain types of cancer, cardiovascular disease, metabolic syndrome, diabetes, sleep disturbance, and psychological distress.[99,145–148] Police specific stressors have been described in multiple ways including inherent dangers, organizational practices, the criminal justice system, and public relations.[149,150]

It is estimated that upwards of 29% of U.S. worker's schedules are outside of a typical daytime work schedule of 0600-1800.[10] Shiftwork may consist of early morning, evening, night, or rotating shifts. Shiftworkers frequently work in service industries such as healthcare, retail, commercial, and financial industries. Shiftwork is also a critical aspect of military service and law enforcement.[11,12] Previous research has also shown shiftwork to be associated with increased incidence of various health conditions including cardiovascular disease, metabolic disorders, gastro-intestinal disorders, and mental disorders.[13–15] Shiftwork frequently causes individuals to sleep at inappropriate times leading the rearrangement of the awake and sleep times. These changes can lead to

dysregulation of the circadian rhythms that may lead to negative effects on various physiological, psychological, and social processes.[146,151,152]

Despite the obvious health effects of shiftwork, there are individuals who appear to tolerate shiftwork better than others. Andlauer et al., first introduced the concept of shiftwork adaptation in 1979, and defined it as the ability to adapt to shiftwork without adverse consequences.[16] Previous work suggests that factors such as circadian type, sleep flexibility, positive affect, family and social relationships, and low work demands are associated with adaptation to shiftwork.[153–155]

While the concept of shiftwork tolerance or adaptation has been previously explored, there is currently no official definition of shiftwork adaptation or tolerance; however, many operationalize shiftwork adaptation or tolerance as an absence of shiftwork associated fatigue, gastro-intestinal troubles, sleep disruption, or changes in behavior.[17,18] Additionally, only a few studies have explored shiftwork adaptation in police officers; however, to our knowledge no studies have explored the framework of shiftwork adaptation using latent analysis in a sample of police officers.[69,156–158]

Thus, the current study has three aims: (1) to identify the predominant subgroups that characterize adaptation to shiftwork among police officers who are participants of the Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) study; (2) to evaluate a broad range of potentially modifiable as well as non-modifiable (or potential confounding) risk factors, personality traits, and lifestyle behaviors that may predict adaptation to shiftwork; (3) to compare multiple biomarkers to include inflammatory,

heart rate variability indices, and cardiometabolic risk characteristics among the resultant latent classes.

4.3 Material and Methods

Study population and procedures

The current analysis comprises police officers working in the Buffalo, New York Police Department who were participants of the Buffalo Cardio-Metabolic Occupational Police (BCOPS) study. The BCOPS study was a prospective population-based study that aimed to investigate the associations of occupational stressors with the psychological and physiological health of police officers.[23] A total of 710 police officers who worked in the Buffalo, New York Police Departments were invited to participate in the study of which 464 officers agreed to participate and were examined between June 4, 2004 and October 2, 2009. Participants were evaluated during a clinical visit scheduled during a training day or day off. Questionnaires were administered to collect information on demographics such as age, gender, education, rank, psychosocial factors, and lifestyle behaviors. Officers also were asked to provide a detailed medical history and to self-report current medication usage. Additionally, 12-hour fasting blood samples were collected by a certified phlebotomist. Specifics regarding recruitment, data collection, and methods are described elsewhere.[23,147] All measures were collected during an off day and not directly following an afternoon or night shift. For the purposes of the proposed study, 242 participants who worked primarily afternoon or night shifts were utilized in latent class analysis; however, for the analyses comparing inflammatory, HRV, and cardiometabolic measures day workers were also included for a total sample size of 430 participants. The BCOPS study received Institutional Review Board approval from The State University of

New York at Buffalo and the National Institute for Occupational Safety and Health. All officers provided written informed consent.

Measures

Shiftwork. Daily shiftwork histories were obtained from electronic payroll records for each officer from 1994 or the start of employment to the date of study participation between 2004 and 2009.[55] Total hours worked as well as hours worked during the day, afternoon, evening shifts were computed for each participant. All shifts were categorized into day, afternoon, or nights according to the following start times of the shifts: 04:00-11:59 (morning), 12:00-19:59 (afternoon), or 20:00-03:59 (night). Long-term shiftwork was defined as the shift that officers spent a majority of their time. For this analysis, only officers whose dominant shift were afternoon or night shifts were included. Even though officers worked fixed shifts, officers occasionally worked for an absent colleague or changed shifts during a work cycle. A typical work cycle consisted of 4 days on, 4 days off, 4 days on, and 3 days off. Therefore, the total number shift changes were collected as officers occasionally work outside of their "normal" shifts Previous work indicated that for >85% of officers, >70% of their time was spent on one shift type.[159]

Sleep. Sleep was measured using the Pittsburgh Sleep Quality Index (PSQI). The PSQI was developed and validated by Buysee and colleagues.[160] The PSQI consists of nineteen self or bed partner rated questions that are used to characterize seven components of sleep quality that include: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep duration, use of sleep medication, and daytime

dysfunction.[160] For the purposes of scoring only self-rated questions were used. Component scores are scored ranging from 0-3. A score of 0 indicates no difficulty, while a score of 3 indicates severe difficulty. For this analysis scores ≥2 represent a poor response for individual sleep components. The global sleep score is a composite score of the seven component scores ranging from 0-21 with 0 score indicating no difficultly and 21 indicating severe difficulty in all component areas. Global sleep score > 5 is considered the cutoff value for poor overall sleep quality.[160,161]

Spielberger Police Stress Survey. The Spielberger Police Stress Survey (SPSS) is a 60-item measure for assessing specific sources of stress in police work.[150] For each event, stressfulness of experiencing the event is rated on a scale ranging from 0-100, 0 representing no stress and 100 representing maximum stress. The mean rating was then calculated for each officer and reported as the total stress rating. Additionally, three subscales were calculated: administrative and organizational pressure which measures satisfaction with departmental policies and procedures, fairness of rewards, performance, and the judicial system; physical and psychological threat which measures dangerous situation and experiences; and lack of support which includes political pressures and relationships with supervisors and coworkers. The subscales have acceptable and consistent scores, Cronbach's alpha > 0.90.[150]

Perceived Stress Scale. Perceived stress (PSS) was measured using the 10-item Perceived Stress Scale (PSS), which is a validated and widely used instrument that measures perception of stress.[162] Perceived stress is calculated by summing all item responses that range in scores from 0-5 (Never, Almost Never, Sometimes, Fairly Often, and Very Often).[162] Higher scores represent higher levels of perceived stress.

Vital Exhaustion. Vital exhaustion (VE) was assessed using the 10-item Maastricht Questionnaire. Vital exhaustion has three dimensions to include: 1) feelings of excessive fatigue and lack of energy, 2) increasing irritability, and 3) feelings of demoralization. The scale has been used previously as a measure of vital exhaustion and predictor of myocardial infarction.[163]

Personality Traits. Personality traits were measured using the NEO Five-Factor Inventory (NEO-FII) and is based on the big five personality trait model.[164,165] The NEO-FII is a shortened version of the NEO Personality Inventory and consists of 60 questions and includes the 12 strongest traits for each subscale (neuroticism, openness to experience, extraversion, conscientiousness, and agreeableness) of the NEO Personality Inventory. Each item is rated on a five-point Likert scale ranging from strongly disagree to strongly agree.

Hardiness. Hardiness was measured using the 15-item developed by Barton et al. [166] The scale is comprised of three dimensions to include control, commitment, and challenge. The control dimension characterizes one's belief that they are capable of managing potentially stressful events. The commitment dimension characterizes one's ability to find meaning in potentially stressful events. The challenge dimension characterizes one's ability to interpret potentially stressful events as opportunities. Each item is rated on a four-point Likert scale that ranges from not at all true to completely true. Summary scores are obtained by reverse coding the appropriate item for the specified dimension. A score for overall hardiness is obtained by summing all 15 items.

Family Environment Scale. The Family Environment Scale (FES) is a 90-item measures that assesses perceived family interactions using three dimensions

(relationships, personal growth, and system maintenance) of the family and its social environment.[167] This scale is comprised of 10 subscales to include cohesion, expressiveness and conflict, independence, achievement orientation, intellectual-cultural orientation, active-recreational orientation, moral religious emphasis, and organization and control. Each subscale is answered using a true/false format. Total scores (range 0-9) are obtained by adding each value in the respective subscale. Higher scores indicate a higher degree of perceived family interaction for the specified dimension. Internal consistency for each subscale ranged from .64 to .79.

Blood measures. Standard laboratory assays were performed to quantify inflammatory (c-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-A (TNF-A), and fibrinogen), cardiometabolic biomarkers (high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, fasting glucose, insulin, adiponectin, and leptin). Fasting blood samples were obtained from all participants by a trained phlebotomist. The samples were sent to Millard Fillmore Laboratory, Buffalo, NY; however, IL-6 and CRP were measured at the University of Vermont from specimens stored at -80°C. The assay range for CRP is 0.16-1100 mg/L. Expected values for CRP in healthy individuals are ≤3 mg/L. Inter-assay coefficients of variation (CV) ranged from 2.1% to 5.7%. IL-6 was measured using a solid-phase quantitative sandwich enzyme-linked immunosorbent assay (ELISA) provided by R&D Systems, Inc., Minneapolis, MN. The IL-6 assay as a low detection range of 0.16 with an upper detection range between 10.0 and 12.0 pg/mL. The normal range for IL-6 is 0.24-12.5 pg/mL and the inter-assay CV range from 8% to 12%. Five percent of all samples were also sent for quality control purposes. Insulin was measured from fasting blood sample specimens

using a chemiluminescent microparticle immunoassay (CMIA) test using the ARCHITECT il000SR System. The normal range for insulin is 2-20uu/mL. Cardiometabolic biomarkers were measured using the Beckman Coulter LX20 clinical chemistry analyzer.[168] Specifics regarding the collection of blood measures are explained elsewhere.[169]

Heart Rate Variability Measures. Heart Rate Variability (HRV) measures were derived using electrocardiograms (ECG) in accordance to a standardized protocol.[170] Specifics regarding the assessment of HRV have been published elsewhere.[171] ECG measures were obtained from a three-electrode lead setup during the carotid ultrasound examination that occurred during the BCOPS clinic examination. Participants were supine and resting for 5 minutes prior to ECG data being collected. Time of the recordings varied from 9:15am to 12:00pm depending on the participants scheduled clinic visit. Each time series was processed using an automated data adaptive QRS detection package. Data editing included visual inspection of the ECG time series overlaid with QRS markers and hand editing of R wave makers where needed. The resultant RR time series were processed using cubic spline interpolation to provide a time series with equal sample increments of two samples per second. The interpolated time series were then detrended using a smoothness priors method.[172] Data were then processed using a parametric autoregressive spectral analysis of order 16.[173] Following these analyses High Frequency (HF) and Low Frequency (LF) components of HRV as well as time domain indices were obtained. HF-HRV is defined as the area under the power spectral density from 0.15 to 0.4 Hz. The LF-HRV is area under the power spectral density between frequencies of 0.04 to 0.15Hz. SDRR is the standard deviations of all

RR intervals. RMSSD is the square root of the mean squared differences of successive RR intervals.

Metabolic Syndrome. The presence of metabolic syndrome was based on the National Cholesterol Education Program Adult Treatment Panel guidelines. Individual components include waist circumference, HDL, triglycerides, hypertension, and measures of glucose intolerance.[44] The presence of at least 3 components is considered diagnostic for metabolic syndrome.[44]

Covariates. Participants completed self and interviewer administered questionnaires to provide information on sociodemographic (age, sex, race, years of service, and education), lifestyle behaviors (alcohol consumption, dietary factors, tobacco consumption, and physical activity) and medical history. Officers reported their highest level of education attained that ranged from ≤12 years of school to graduate degrees, the number of years employed as police officer, and current rank (Police Officer, Sergeant/Lieutenant/Detective). Participants were also asked how often they consumed alcoholic beverages that consisted of a 12oz can or bottle of beer, medium glass of wine, or one shot of liquor. The total number of drinks per month was summed and divided to give the approximate total number of drinks consumed per week. Work activity was reported as the duration (hours per week and hours per weekend) and intensity (moderate, hard, and very hard) for occupation physical activity during the previous seven days. Work activity was further dichotomized as high work activity vs low or moderate activity.

Data analysis

Analyses were performed using SAS 9.4 (Cary, North Carolina, USA) and R version 3.5.0. Latent class variable selection procedures were conducted using the R-package *LCAvarsel version 1.1* and subsequent LCA analyses were conducted using the SAS procedure *PROC LCA*.[174,175] Descriptive statistics were evaluated using frequencies and chi-square tests for categorical variables. For continuous variables means and standard deviations were presented, and tests of significance were estimated using independent t-tests or Wilcoxon ranks sums test based on the normality of the variable. A confounder selection process was utilized prior to the main analyses. Covariates with a p-value ≤0.20 in bivariate analyses were added to full model for the both the generalized linear (GLM) and logistic regression models and a confounder reduction process was conducted. Covariates were removed one at a time and those that changed the effect estimate of interest (latent class membership) by at least 10% or remained statistically significant with a p-value ≤0.05 were kept in the model. A backwards model selection procedure was utilized to determine the final risk prediction model, and variables with p-values ≤0.05 were retained in the final model. Linear regression assumptions were evaluated by examining the final model's residuals.

Variables included in the latent class model. There are no restrictions on the number of indicator variables that can be entered into a latent class model.[176] In general, higher quality indicators, more indicators, and larger sample sizes lead to a model that is more likely to converge.[176] Initially, twenty-two variables were chosen a-priori based on a review of the shiftwork adaptation literature and the measures available in the BCOPS study. Variable selection was then conducted using a swap-stepwise procedure based on

the work of Fop et al. and Rafferty et al.[174,177] This method is based on the comparison of two different models, and allows the removal of variables that provide no clustering information as well as those that carry redundant information. The goal of the variable selection is to retain indicator variables which contain the most useful clustering information. Apart from the vital exhaustion measures all the self-reported measures were on a continuous scale and were subsequently dichotomized. The following variables were selected as indicator variables: 1) Sleep disturbance (PSQI) is scored on 4-point Likert scale ranging from 0-3. For this analysis the sleep disturbance component was dichotomized using a cut-off value of ≥ 2; 2) Sleep latency (PSQI) is scored on 4-point Likert scale ranging from 0-3. For this analysis the sleep latency component was dichotomized using a cut-off value of ≥2 (>30 min). 3) High lack of support is a subscale of the Spielberger Police Stress Survey and consists of 13-items that measure political pressures and relationships with supervisors and coworkers. For this analysis participants in the highest quartile are considered to have a high lack of support. 4) High perceived stress is measured on a 5-point Likert scale ranging from 0-4. For this analysis participants in the highest quartile are considered to have high perceived stress. 5-8) Individual questions from vital exhaustion (feel more listless than before joining law enforcement, sometimes feel that your body is like a battery that is losing its power, feel dejected, and frequently experience a sense of exhaustion at work). A yes response indicates a maladaptive or poor response. Description of indicator variables are presented in Table 4.4.

Latent class model development. The purpose of the latent class analysis is to identify subgroups of individuals who are alike in their response to the categorical

indicator variables.[175,178,179] Latent class models were fitted consecutively starting with a two-cluster model. The optimal number of clusters was determined primarily by the interpretability and parsimony of the model; however, several other criteria were also considered to include: 1) Goodness of fit statistics: Bayesian Information Criterion (BIC) and bootstrapped parametric likelihood test. A model with a lower BIC is preferred and the bootstrapped parametric likelihood ratio test assesses if the addition of a single cluster significantly improves the model fit.[180] 2) Classification uncertainty: Entropy measures the distinction between class. Values range from 0-1 with scores closer to one being considered optimal. Values that ≥0.70 indicate adequate separation of clusters.[181] 3) At least 10% of the sample in each cluster.

Comparison of latent classes. GLM procedures and chi-square tests were conducted to compare a broad range of potentially modifiable as well as non-modifiable (or potential confounding) risk factors, personality traits, and lifestyle behaviors that may predict adaptation to shiftwork. GLM procedures also were used compare inflammatory, heart rate variability indices, and cardiometabolic risk characteristics among the resultant latent classes. The GLM procedure allows for the estimation of least square means and 95% confidence intervals of various predictor, inflammatory, HRV, and cardiometabolic risk factors based on latent class membership. Multivariable logistic regression analyses were conducted to develop a risk-prediction model that examines various demographic, lifestyle, and trait like factors associated with latent class membership. Logistic regression can be used for the estimation of odds ratios, 95% confidence intervals, and p-values. Lastly, to further test the predicative capability of the variables included in the risk prediction model on predicting membership to the shiftwork adapted group versus

the shiftwork maladapted group, an area under receiver operating characteristics (AUC ROC) curve analysis was performed using logistic regression. In general, AUC ROC ≥0.9 is considered outstanding in ability to differentiate between predictive variables, 0.8 ≤AUC ROC < 0.9 is considered excellent; whereas, ≤0.7 AUC ROC <0.8 is considered adequate, and AUC ROC below 0.7 is considered to have poor predictive value.[124]

4.4 Results

Demographic Characteristics. The study population was comprised of 242 polices officers who worked primarily afternoon or night shifts. Mean age of the sample was 40±7.1 years. The study population was primarily white (84%), male (86%), and married (75%). Most of the study population had more than a high school (89%) education and an annual income (71%) over $70,000. The average number of years employed as police officer was 13.4±7.1 years, and majority of the sample held the rank of police officer (78%). The study population characteristics are presented in Table 4.1.

Latent Class Analysis. Serial latent class analyses were conducted that specified 2-5 classes. Based on interpretability of the model the 2-class model was chosen. Additionally, the best model as indicated by BIC and bootstrapped likelihood ratio tests was the 2-class model. The entropy for this class was highest (0.85) among the four compared models, and according to the Bootstrap Likelihood Ratio Test (2 class vs 3 class, p-value = 0.18) the addition of another class did not increase the overall fit of the model. Model fit indices for each model are presented in Table 4.2. As shown in Table 4.3 and Figure 4.1, the selected 2-class model included a class of individuals (shiftwork maladapted, n = 73) who had a moderate-high probability of self-reported sleep disturbances ≥2 times per week (PSQI) in last 30 days, sleep latency > 30min (PSQI) in

the last 30 days, high lack of support (SPSS), high perceived stress, and symptoms of fatigue (vital exhaustion); whereas, the other class (shiftwork adapted, n= 169) had relatively low probability of those characteristics. A description of the latent class indicator variables is presented in Table 4.4.

Comparison of classes. After identifying the latent classes, individuals were assigned to their most likely class membership based on their posterior probabilities. Group comparisons were then conducted using GLMs or chi-square tests as appropriate. There were no statistically significant differences between the shiftwork adapted and maladapted groups on the bases of age, sex, race, income, or education. However, there were significant differences on the bases of marital status and dietary factors, specifically fruit and vegetable consumption. Results are presented in Table 4.5.

As expected the shiftwork adapted group had higher mean levels of extraversion agreeableness, conscientiousness, hardiness, family independence, active-recreational orientation and family organization, compared to the maladapted group. In addition, the shiftwork adapted group had lower levels of neuroticism and family conflict. There were no differences in openness, family control, or number of children. Results are presented in Table 4.6.

Predictors of latent class membership. In the multivariable prediction model only, hardiness and high vegetable consumption were predictors of adaptation. Whereas, neuroticism and family conflict were inversely associated with shiftwork adaptation. Results are presented in Table 4.6. Results from the AUC ROC analyses are presented in Figure 4.2. The full model (AUC = 0.84, 95% CI = 0.78-0.89) demonstrated excellent predictive capability. Individually, hardiness and neuroticism demonstrated adequate

ability to predict membership into the shiftwork adapted group; whereas, vegetable consumption and family conflict demonstrated poor predictive capability.

Comparison of inflammatory measures. In general, police officers who primarily work day shifts had levels of inflammatory markers that were similar to the adapted group (Table 4.7). Interleukin-6 concentrations (0.50±0.05) were lower in the dayshift group relative to the maladapted group (0.81±0.08), but there were no differences between the adapted and maladapted groups (Table 4.7).

Comparison of heart rate variability measures. There were no differences in HRV between the adapted, maladapted, or day shiftworkers (Table 4.8).

Comparison of cardiometabolic risk factors. Police officers in the adapted shiftwork group had lower diastolic blood pressure (77.52±1.00) than the maladapted group (80.25±1.29). Both the adapted (9.35±0.07) and day shift (9.42±.00) group (9.64±0.09) had lower levels of leptin than the maladapted group (Table 4.9).

4.5 Discussion

The current study identified two subgroups among officers from the BCOPS study; one characterized as adapted to shiftwork (70%) and another maladapted (31%) using eight indicator variables from the PSQI, SPSS, PSS, and VE instruments. The adapted group reported lower probabilities of having a poor response to the measures of sleep, stress, and chronic fatigue. Additionally, officers in the adapted group were slightly older, had better diets, higher levels of extraversion, agreeableness, hardiness, and lower levels of neuroticism. The adapted group also tended to have more family independence and organization, and less family conflict. There were no differences in inflammatory, HRV, or cardiometabolic risk factors between the latent classes for police officers except

for diastolic blood pressure and leptin. However, in the general analysis approach we observed higher in mean levels of IL-6 and TNF-A in maladapted officers in comparison to dayshift officers (Appendix B: Table B.6). Again, there were no differences in inflammatory, HRV, or cardiometabolic risk factors between the latent classes for police officers and day shiftworkers with the exception insulin (Appendix B: Table B.6-B.8).

The central role of age, gender, circadian misalignment, sleep, positive and negative moods, and personality have been explored in multiple studies; however, these studies varied in their research methodology.[18,69,182,183] In the current analysis, we used state-like variables to specify the latent classes, and trait-like variables as potential predictors of latent class membership. Adaptation to shiftwork was associated with several personality traits and perceived family interactions. These findings are consistent with previous studies that reported high neuroticism, low extraversion, and less positive affect among maladapted shiftworkers.[69,184,185] Young age was associated with adaptation to shiftwork and tolerance to shiftwork tends to decrease between the ages of 40 and 50.[186,187] A recent systematic review of shiftwork tolerance reported that the majority of cross-sectional and longitudinal studies found that female shiftworkers have more sleep problems, fatigue, disability, issues with coping, and metabolic dysregulation in comparison to male shiftworkers.[18] In another study examining shiftworkers tolerance in a group of nurses using principal component analysis procedures found two factors that characterized shiftwork tolerance: well-being and physical health.[60] While this study utilized a different analysis approach, our results were consistent overall in that depression, sleep disturbance, fatigue, and stress were related to shiftwork tolerance.

This study has some limitations to include a modest sample size, potential healthy-worker survival effect, and the lack of a direct question or instrument examining shiftwork related problems such as the Standard Shiftwork Index.[166] The healthy-worker survival effect is a bias that occurs in occupational studies when less healthy workers are more likely to reduce their work place exposure. The average time in service of officers in the present study was 13.9 years, meaning that officers who were unlikely to tolerate shiftwork may have already left police service. The implications to the present study is that our results are more likely to be biased towards the null. Furthermore, this may elucidate as why the majority of the sample (70%) were characterized as adapted to shiftwork. Data on factors known to be associated with shiftwork adaptation, such as circadian type/morningness and genetic information, were unavailable for the current study. For example, morningness is related to shiftwork maladaptation.[18] Additionally, this study is limited as all the indicator variables are self-report measures that were collected cross-sectionally and susceptible to temporal variability.

Despite the limitations there are some noteworthy strengths. All the physical and blood measures were performed in a clinical setting by trained clinical personnel following a standardized protocol. Another strength in this evaluation is the ability to adjust for important confounders such as race, education, gender, alcohol use, physical activity, and medications that may affect PNS activity. Lastly, the present analysis may be generalizable to similar populations such as military personnel, firefighters, and other first responders.

In conclusion we utilized latent class analysis to identify the prominent subgroups that characterize adaptation to shiftwork among participants of the BCOPS study. We

found that officers who reported poorer sleep, high stress, and chronic fatigue were less likely to be adapted to shiftwork. Overall, there were no differences in term of inflammatory and cardiometabolic biomarkers and HRV measures; however, our results suggest that adapted officers had similar biomarker profiles to dayworkers in comparison to maladapted night workers. To our knowledge, this is the first study to use latent class analysis procedures to characterize shiftwork adaptation among police officers and examine differences in inflammatory, HRV, or cardio-metabolic biomarkers between adapted and maladapted shiftworkers. Future studies evaluating the association between shiftwork adaptation and clinical biomarkers may be enhanced by the use of prospective study designs, increased sample sizes, and the addition of measures that examine circadian rhythm misalignment.

Table 4.1 Demographic characteristics of study participants, BCOPS Study, Buffalo, NY, USA, 2004-2005 (n=242)

Characteristic	Overall (n=242)
	Mean (SD) or n (%)
Age, (Years)	40.0 (7.1)
Gender	
Male	209 (86.4)
Female	33 (13.6)
Race	
White	200 (84.0)
Non-White	38 (16.0)
Marital Status	
Single	27 (11.3)
Married	179 (74.6)
Divorced	34 (14.2)
Education	
≤12 Years	26 (10.8)
College < 4 Years	127 (52.7)
College ≥4 Years	88 (36.5)
Rank	
Police Officer	160 (78.3)
Sergeant/Lieutenant/Captain	30 (13.0)
Detective/Executive/Other	20 (8.7)
Years of police service	
0-9 Years	81 (33.6)
10-14 Years	64 (26.6)
15-19 Years	49 (20.3)
20+ Years	47 (19.5)
Income	
<$70,000	54 (23.0)
$70,000 – $90,000	77 (32.8)
$90,000+	104 (44.3)
Percentages not totaling 100% are due to rounding or missing data.	

Table 4.2 Fit statistics for latent class models

Table 4.2 Fit statistics for latent class models							
Number of Classes	Residual df	AIC	BIC	G^2	Entropy	BS-LRT	%Solution
2	238	204.03	263.34	30.42	0.85	--	100.0
3	229	201.86	292.57	149.86	0.69	0.18	60.60
4	220	205.62	327.73	135.62	0.72	0.60	73.8
5	211	211.76	365.27	123.76	0.72	0.83	57.4
Abbreviations: df = degrees of freedom; AIC = Akaike Information Criterion; BIC= Bayesian Information Criterion; G^2= Likelihood-ratio chi-square statistic; BS-LRT=Bootstrap Likelihood Ratio Test; %Solution – Percentage of seeds associated with best fitted model.							

Table 4.3 Prevalence of latent class membership and item-response probabilities among police officers, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

Latent Class Characteristics	Latent Class Membership	
	Shiftwork Maladapted (n=73)	Shiftwork Adapted (n=169)
Probability of class membership	0.31	0.70
Conditional probability of a poor response		
Sleep Disturbance ≥ twice per week[1]	0.55	0.19
Sleep Latency >30 min[1]	0.55	0.27
High Lack of Support[2]	0.41	0.16
High Perceived Stress [3]	0.66	0.07
Feel more listless than before joining law enforcement [4]	0.79	0.10
Sometime feel that your body is like a battery that is losing its power[4]	0.94	0.23
Feel dejected[4]	0.33	0.0003
Frequently experience a sense of exhaustion at work[4]	0.68	0.13
[1]Indicator variable was derived from a component of Pittsburg Sleep Quality Index. [2]Indicator variable is a subscale of the Spielberger Police Stress Survey. [3]Indicator variable was derived from the Perceived Stress Scale. Officers in the highest quartile are considered to have high perceived stress. [4]Indicator variables are individual items from the Vital Exhaustion scale.		

Table 4.4 Description of latent class analysis indicator variables

Sleep Disturbance ≥ twice per week	Sleep disturbance is a component of the PSQI, which is a 19 item self-administrated questionnaire that evaluates sleep quality over a one-month period. [160] Sleep disturbance is scored on 4-point Likert scale ranging from 0-3. For this analysis the sleep disturbance component was dichotomized using a cut-off value of ≥2.
Sleep Latency >30 min	Sleep latency is a component of the PSQI, which is a 19-item self-administered questionnaire that evaluates sleep quality over a one-month period. [160] Sleep latency is scored on 4-point Likert scale ranging from 0-3. For this analysis the sleep latency component was dichotomized using a cut-off value of ≥2 (>30 min).
High Lack of Support	Lack of support is a subscale of the Spielberger Police Stress Survey and consists of 13 items that measure political pressures and relationships with supervisors and coworkers.[150] For this analysis participants in the highest quartile are considered to have a high lack of support.
High Perceived Stress	Perceived stress is measured using the Perceived Stress Scale, which is a 14-item scale that measures the frequency of stressful events and experiences during the previous month.[162] Perceived stress is measured on a 5-point Likert scale ranging from 0-4. For this analysis participants in the highest quartile are considered to have high perceived stress.
Feel more listless than before joining law enforcement.	A component of the vital exhaustion scale. A yes response indicates a poor or maladaptive response.
Sometimes feel that your body is like a battery that is losing its power.	A component of the vital exhaustion scale. A yes response indicates a poor or maladaptive response.
Feel dejected.	A component of the vital exhaustion scale. A yes response indicates a poor or maladaptive response.
Frequently experience a sense of exhaustion at work.	A component of the vital exhaustion scale. A yes response indicates a poor or maladaptive response.
Abbreviations: PSQI = Pittsburgh Sleep Quality Index.	

Table 4.5 Individual predictors of shiftwork adaptation, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

Variables	Latent Class Membership		p-value
	Adapted (n=169)	Maladapted (n=73)	
	%	%	
Age			
<40 years	50.9	54.8	0.58
≥40 years	49.1	45.2	
Race			
White	82.6	87.3	0.37
Non-White	17.4	12.7	
Sex			
Male	88.2	82.2	0.22
Female	11.8	17.8	
Marital Status			
Single	8.3	18.1	0.06
Married	78.6	65.3	
Divorced	13.1	16.7	
Income			
<$70,000	22.8	23.3	1.00
$70,000 – $90,000	32.7	32.9	
$90,000+	44.4	43.8	
Years of Police of Service			
0-9	33.9	32.9	0.33
10-14	28.0	23.3	
15-19	17.3	27.4	
20+	20.8	16.4	

Table 4.5 Individual predictors of shiftwork adaptation, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242) (continued)

Variables	Latent Class Membership		p-value
	Adapted (n=169)	Maladapted (n=73)	
	%	%	
Rank			
Police Officer	79.4	75.7	0.73
Sergeant/Lieutenant/Captain	11.9	15.7	
Detective/Executive/Other	8.6	8.6	
Work Activity			
High	31.0	63.0	0.70
Low-Moderate	69.1	37.0	
Education			
≤12 Years	10.7	11.0	0.89
College < 4 Years	51.8	54.8	
College 4+ Years	37.5	35.3	
Tobacco Use			
Never	53.9	50.7	0.52
Former	17.4	13.7	
Current	28.7	35.6	
Servings of food cooked in fat per day			
High	27.8	38.4	0.11
Low	72.2	61.6	
Servings of vegetables per day			
High	69.8	50.7	<0.01
Low	30.2	49.3	
Servings of fruit per day			
High	89.4	75.3	<0.01
Low	10.6	24.	

Each predictor was run as a separate bivariate model.

Table 4.5 Individual predictors of shiftwork adaptation, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242) (continued)

Variables	Latent Class Membership		p-value
	Adapted (n=169)	Maladapted (n=73)	
	Mean ± SD	Mean ± SD	
Age, years	40.6 ± 7.4	38.8 ± 5.9	0.05
Neuroticism[a]	12.4 ± 5.0	19.6 ± 7.7	<0.01
Extraversion[a]	30.1 ± 5.6	26.8 ± 6.0	<.001
Openness[a]	23.5 ± 5.4	23.2 ± 4.7	0.74
Agreeableness[a]	31.6 ± 5.0	29.2 ± 5.2	<0.01
Conscientiousness[a]	34.1 ± 5.4	30.1 ± 7.0	<.001
Hardiness[a]	29.3 ± 4.3	24.9 ± 5.4	<0.01
FES-Conflict[b]	2.2 ± 1.9	3.3 ± 2.4	<0.01
FES-Independence[b]	7.0 ± 1.4	6.4 ± 1.4	<0.01
FES-Active-Recreational Orientation[b]	6.2 ± 1.9	5.4 ± 2.1	<0.01
FES-Organization[b]	6.6 ± 2.0	5.2 ± 2.4	<0.01
FES-Control[b]	5.0 ± 1.9	5.2 ± 2.1	0.69
Number of Children	2.5 ± 1.2	2.9 ± 1.5)	0.16
PSQI- Global Sleep Score	5.7 ± 2.9	8.6 ± 2.7	<0.01
Abbreviations: SD = Standard Deviation, FES = Family Environment Scale, PSQI = Pittsburgh Sleep Quality Index. [a]Higher scores represent more extraversion, agreeableness, openness, conscientiousness, or hardiness. [b]Higher scores correspond to more family independence, active-recreational orientation, conflict, control, or organization. Each predictor was run as a separate bivariate model.			

Table 4.6 Multivariable predictors of shiftwork adaptation, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

Variables	OR (95% CI)	p-value
Servings of vegetables per day		
High	2.57 (1.10-5.98)	0.03
Low	Ref	
Neuroticism[a]	0.85 (0.79-0.92)	<0.01
Hardiness[a]	1.13 (1.03-1.25)	0.01
FES-Conflict[b]	0.73 (0.60-0.88)	<0.01
Reference Group = Maladapted Group Abbreviations: OR = Odds Ratio; CI = Confidence Interval; Ref = Reference. [a]Higher scores represent more extraversion, agreeableness, openness, conscientiousness, or hardiness. [b]Higher scores correspond to more family independence, active-recreational orientation, conflict, control, or organization.		

Table 4.7 Mean (Standard Error) levels for Inflammatory measures by Latent Class Membership, BCOPS study, 2004-2005 (n=430)

Inflammatory Measures	Latent Class Membership		Day shift (n=188)	p-value[a]
	Adapted (n=67)	Maladapted (n=156)		
Ln C-Reactive Protein (mg/l)	0.72±0.10	0.72±0.13	0.57±0.09	0.39
Ln Interleukin-6 (pg/ml)	0.66±0.06	0.81±0.08	0.50±0.05*	<0.01
Tumor Necrosis Factor-A (mg/ml)	4.90±0.19	5.28±0.26	4.88±0.15	0.31
Fibrinogen (mg/dl)	318.15±5.49	308.74±8.35	311.83±5.36	0.56

[1]Model adjusted for age, gender, BMI, and marital status. [2]Model adjusted for age, gender, BMI, and alcohol. [3]Model adjusted for age, gender, race, and BMI. [4]Model adjusted for age. [a]Overall p-value for variable of interest. *p≤0.05 versus maladapted group. Abbreviations: SE= Standard Error, Ln = Natural Log, BMI = Body Mass Index (kg/m^2).

Table 4.8 Mean (Standard Error) levels for HRV measures by Latent Class Membership, BCOPS study, 2004-2005 (n=430)

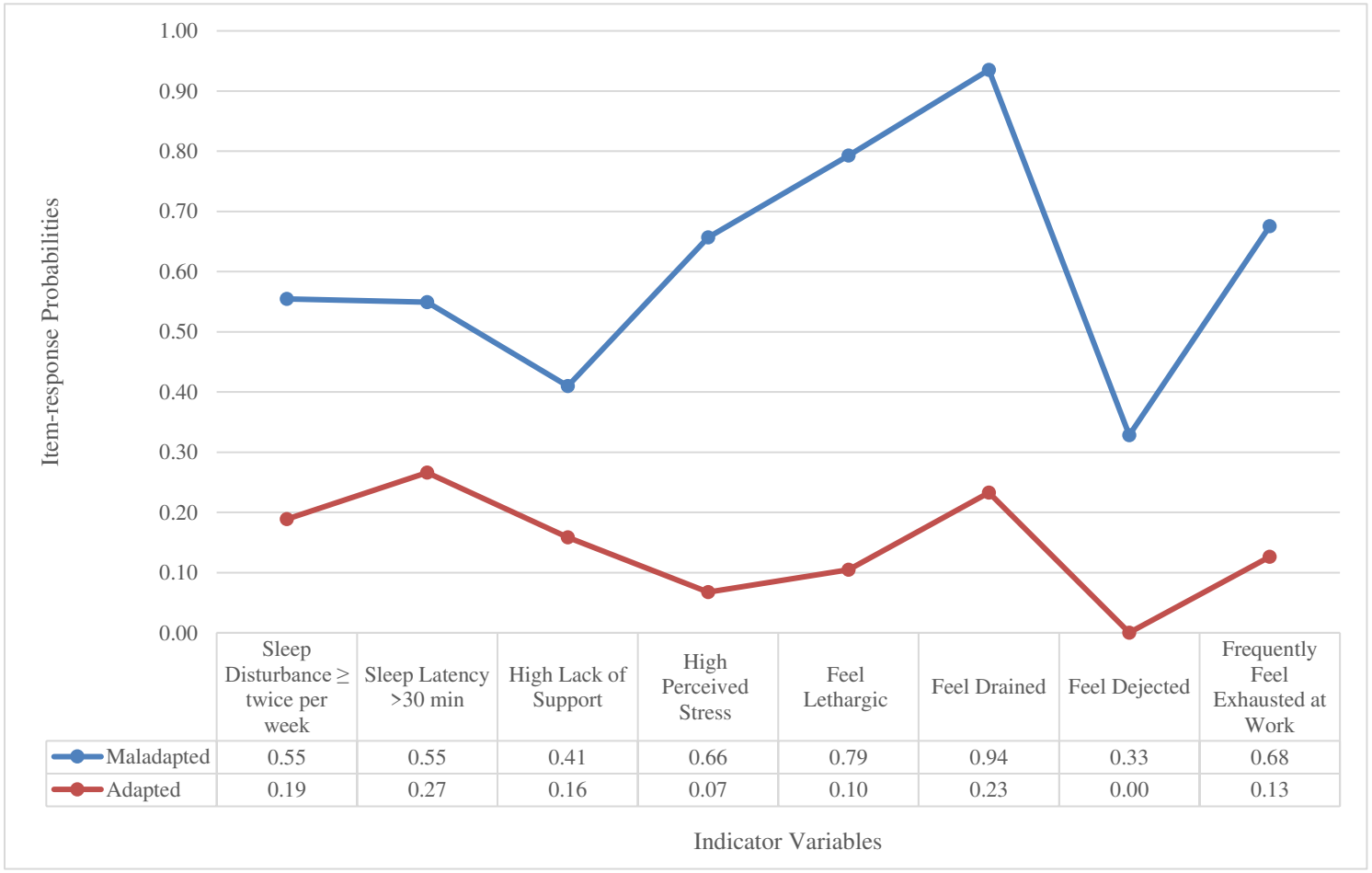
HRV Measures	Latent Class Membership		Day shift (n=188)	p-value[a]
	Adapted (n=67)	Maladapted (n=156)		
Ln SDNN (ms)	3.32±0.04	3.27±0.05	3.28±0.04	0.61
Ln RMSSD (ms)	3.67±0.06	3.59±0.07	3.57±0.06	0.22
Ln HF-HRV (ms^2)	4.71±0.13	4.93±0.15	4.83±0.12	0.35
Ln LF-HRV (ms^2)	5.19±0.08	5.27±0.12	5.21±0.07	0.80

[1]Model adjusted for age, physical activity, BMI, and antidepressants. [2]Model adjusted for age, physical activity, BMI, and antidepressants. [3]Model adjusted for age, sex, physical activity, and antidepressants. [4]Model adjusted for age, gender, physical activity, and BMI. [a]Overall p-value for variable of interest. *p≤0.05 versus maladapted group. Abbreviations: SE= Standard Error, Ln = Natural Log, HF-HRV = High Frequency Heart Rate Variability (0.15-0.40 Hz), LF-HRV = Low Frequency Heart Rate Variability (0.04-0.15 Hz), SDNN = Standard Deviation of N-N Intervals, RMSSD = Root Mean Square of Successive Differences, BMI = Body Mass Index (kg/m^2), ms = Milliseconds.

Table 4.9 Mean (Standard Error) levels for cardiometabolic measures by latent class membership, BCOPS study, 2004-2005 (n=430)

Cardiometabolic Measures	Latent Class Membership		Day shift (n=188)	p-value[a]
	Adapted (n=67)	Maladapted (n=156)		
High Density lipoprotein (mg/dl)[1]	50.79 ± 1.27	49.04 ± 1.64	50.04 ± 1.12	0.61
Low density protein (mg/dl)[2]	126.10 ± 2.86	131.52 ± 4.17	123.15 ± 2.55	0.20
Ln Triglycerides (mg/dl)[3]	4.40 ± 0.06	4.52 ± 0.08	4.45 ± 0.05	0.31
Glucose (mg/ml)[4]	90.89 ± 1.07	90.91 ± 1.42	91.26 ± 0.93	0.95
Systolic Blood Pressure[5]	122.83 ± 1.03	123.60 ± 1.50	123.60 ± 0.92	0.23
Diastolic Blood Pressure[6]	77.52 ± 1.00*	80.25 ± 1.29	77.57 ± 0.87	0.12
Waist Circumference (cm)[7]	90.8 3 ± 1.44	90.61 ± 1.63	90.97 ± 1.35	0.98
HbA1C, %[8]	5.60 ± 0.04	5.59 ± 0.06	5.66 ± 0.04	0.51
Ln Insulin (uu/ml)[9]	1.83 ± 0.06	1.99 ± 0.08	1.90 ± 0.05	0.22
Adiponectin (ng/ml)[10]	14141.81 ± 652.67	13654.14 ± 848.35	14005.91 ± 549.70	0.85
Ln Leptin (pg/ml)[11]	9.35 ± 0.07*	9.64 ± 0.09	9.42 ± 0.06*	0.01
Metabolic Syndrome Components[12]	1.44 ± 0.12	1.54 ± 0.14	1.57 ± 0.11	0.55

[1]Model adjusted for gender, alcohol, physical activity, marital status, and BMI. [2]Model adjusted for race, physical, activity, and BMI. [3]Model adjusted for gender, race, and BMI. [4]Model adjusted for age, gender, BMI, Tobacco, and education. [5]Model adjusted for age, race, alcohol, and BMI. [6]Model adjusted for age, gender, BMI, and marital status. [7]Model adjusted for age, gender, alcohol, antidepressants, tobacco, and marital status. [8]Model adjusted for age, race, and BMI. [9]Model adjusted for sex, tobacco, and BMI. [10]Model adjusted for age, gender, race, marital status, and BMI. [11]Model adjusted for gender, race BMI, and tobacco. [12]Model adjusted for gender, BMI, and antidepressants. [a]Overall p-value for variable of interest. *p≤0.05 versus maladapted group. Abbreviations: SE= Standard Error, Ln = Natural Log, BMI = Body Mass Index (kg/m^2).



	Sleep Disturbance ≥ twice per week	Sleep Latency >30 min	High Lack of Support	High Perceived Stress	Feel Lethargic	Feel Drained	Feel Dejected	Frequently Feel Exhausted at Work
Maladapted	0.55	0.55	0.41	0.66	0.79	0.94	0.33	0.68
Adapted	0.19	0.27	0.16	0.07	0.10	0.23	0.00	0.13

Figure 4.1 Prevalence of latent class membership and item-response probabilities among police officers, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

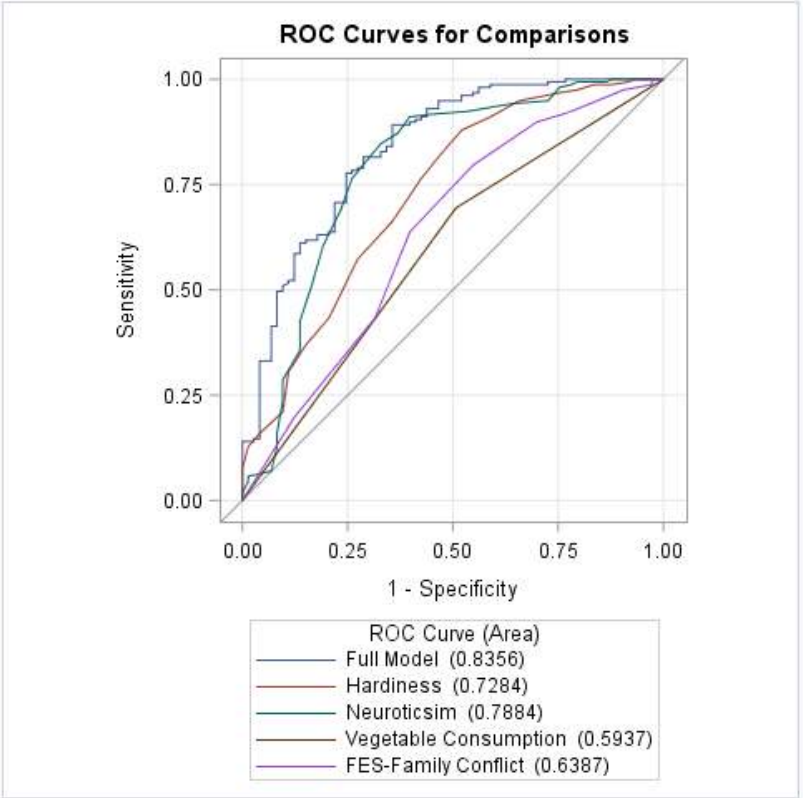


Figure 4.2 Receiver operating characteristic curves for membership to the shiftwork adapted latent subgroup. Full model area under the curve = 0.84; 95% confidence interval: 0.78-0.89; Hardiness area under the curve = 0.73; 95% confidence interval: 0.66-0.80; Neuroticism area under the curve = 0.79; 95% confidence interval: 0.72-0.86; Vegetable Consumption area under the curve = 0.59; 95% confidence interval: 0.53-0.66; FES-Family conflict area under the curve = 0.64; 95% confidence interval: 0.56-0.72.

CHAPTER 5

SLEEP, HEART RATE VARIABILITY, AND METABOLIC SYNDROME [3]

[3] Nevels, T., M. Wirth, A. Mclain, JP. Ginsberg, J.B. Burch. To be submitted to *Chronobiology International or Sleep*.

5.1 Abstract

Introduction. Sleep disruption and autonomic dysfunction characterized primarily as overactivation of the sympathetic (SNS) nervous system may contribute to the development of metabolic syndrome, conferring increased risk of cardiovascular disease and other chronic health conditions. Heart rate variability (HRV) is commonly used to assess autonomic function. Decreased HRV has been associated with increased risk of chronic diseases and all-cause mortality. **Objectives.** This study examined the inter-relationships between self-reported sleep quality, heart rate variability (HRV), and metabolic syndrome in addition to examining the moderating effect of reduced HRV on the association between sleep quality and metabolic syndrome. **Methods.** Data were obtained from 966 participants from the Midlife in The United States II (MIDUS II) survey and biomarker projects. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI). HRV data were ascertained from an 11-minute heart rate recording utilizing a standardized protocol. Generalized linear models and logistic regression were used to examine whether poor sleep or low HRV, both individually and in combination, are associated with metabolic syndrome. **Results.** PSQI sleep score (OR = 1.06, 95% CI = 1.01-1.11) as a continuous and categorical measure (Cut-off > 5, (OR = 1.49, 95% CI = 1.07-2.08) were both associated with metabolic syndrome after adjusting for relevant confounders. There was an inverse association between increasing SDNN (OR = 0.68, 95% CI = 0.48-0.96) and RMSSD (OR=0.77, 95% CI = 0.59-0.99) and metabolic syndrome. Among participants with metabolic syndrome, there was a relationship between poor sleep quality and HRV; however, there was no relationship between sleep quality and HRV among participants without metabolic syndrome. The association

between sleep quality and metabolic syndrome was strengthened among individuals with low HRV (Low-Frequency (LF) HRV Quartile 1: OR=2.00, 95% CI=1.05-3.80), relative to those with elevated HRV (LF -HRV Quartile 2-4: OR=1.31 95% CI=0.89-1.95).

Discussion. To the author's knowledge, this is the first study to examine the moderating effects of HRV on the relationship between sleep quality and metabolic syndrome. Sleep quality and HRV may both influence the development of metabolic syndrome and cardiovascular disease.

5.2 Introduction

The prevalence of poor sleep, specifically short sleep duration, has increased in conjunction with the increased prevalence of metabolic disorders and obesity in United States.[10] Sleep and circadian rhythms play a role in the regulation and optimization of various physiological functions.[12] This suggests a potential relationship between poor sleep and metabolic dysregulation. In a longitudinal analysis of National Health and Nutrition Examination Survey (NHANES) data from 1988-2012, the prevalence metabolic syndrome increased by more than 35% among adults.[24] In a meta-analysis evaluating the relationship between sleep duration and metabolic syndrome, the pooled odds ratios (OR) for metabolic syndrome among those with sleep duration <7 hours was 1.23 (95% CI: 1.11–1.37, p<0.001) compared to individuals with daily sleep duration of 7-8 hours.[25] They also found a decreasing dose response relationship between sleep duration of <5, 5-6 hours, and 6-7 hours and metabolic syndrome respectively.[25] Multiple cross-sectional studies examining self-reported sleep quality have found associations between poor sleep and metabolic syndrome and its individual components; however, due

to the cross-sectional nature of the study designs no causal relationship between poor sleep and metabolic syndrome could be evaluated.[26–28]

While activation of the sympathetic nervous system (SNS) and suppression of the parasympathetic nervous system (PNS) is known to be a key aspect of the pathogenesis of metabolic syndrome and its components, it is not part of the diagnostic criteria for metabolic syndrome. The components (waist circumference >102cm for men and >88cm for women; triglycerides ≥150 mg/dL, high-density lipoprotein <40 for men and <50 for women; blood pressure ≥130/85; or serum glucose ≥110 mg/dL) of metabolic syndrome have been shown to be individually associated with lower HRV.[90–92] For example, Liao and colleagues found that HRV indices were lower in individuals with multiple components of metabolic syndrome.[93] They also found decreasing HRV as the number of individual metabolic syndrome components increased. [93] In another study, Korean adults with metabolic syndrome had lower mean HRV, and all metabolic syndrome components were negatively correlated with HRV. [94]

The objectives of this study were to: (1) Examine the cross-sectional associations between poor sleep quality, low heart rate variability, and metabolic syndrome in a nationally representative sample of U.S. Adults from the Midlife Development in the United States Study; 2) Evaluate to what extent heart rate variability moderates the relationship between poor sleep quality and metabolic syndrome.

5.3 Material and Methods

Study population and procedures.

This study utilized data from the Midlife Development in the United States (MIDUS II) survey II and biomarker projects. The MIDUS II study is a longitudinal

follow up of the first MIDUS study that aimed to investigate the long-term role of behavioral, psychological, and social factors in age-associated physical and mental health outcomes. The MIDUS II biomarker project assessed a subsample of the original respondents to ascertain the biopsychosocial pathways that contribute to physical and mental health metrics. For this analysis, data from 966 participants who had complete heart rate variability, metabolic syndrome components, and sleep measures quantified by the Pittsburgh Sleep Quality Index (PSQI) data were utilized. No participants were excluded on the basis of race, education, gender, or outcome measures. Data elements from the biomarker project were collected during a 24-hour stay at one of three General Clinical Research Centers (GCRC) using a standardized clinical protocol. The protocol included fasting blood samples, 12-hour urine sample collection, a detailed medical history, physical examination, questionnaires, and was conducted on the second day of the participant's GCRC visit. All participants gave their written informed consent and each MIDUS research center obtained institutional review board approval. The original data collection protocol has been previously described.[188] All data elements are publicly available and were downloaded from Inter-University Consortium for political and Social Research website.

Measures

Heart Rate Variability. An HRV psychophysiology protocol was followed during an overnight stay at one of three clinics. Participants were provided a meal; however, they were not permitted to consume caffeine. Electrocardiogram (ECG) electrodes were placed on the left and right shoulder and the lower left chest quadrant. A respiration band was placed around the chest, and a Finometer beat to beat blood pressure cuff was placed

around the middle finger of the participants' non-dominant hand. While participants were in a seated position, data were recorded during an 11-minute baseline assessment, followed by exposure to challenging stimuli and subsequent recovery period. Only baseline HRV data were utilized for this study.

After the collection of analog ECG signals, the data were digitized at a sampling rate of 500 Hz by a 16-bit National Instruments analog to digital board installed in a microcomputer. A custom proprietary software was then used to identify R waves. Research staff visually inspected all ECG waveforms for errors resulting in time and frequency domain indices. Time domain indices included RR interval variability characterized as standard deviation of RR interbeat intervals (SDRR) and root mean square of successive differences in interbeat interval (RMSSD). Frequency domain indices included high (HF-HRV; 0.15-0.50 Hz) and low (LF-HRV; 0.04-0.15Hz) spectral power frequency bands. Spectral domains were calculated using interval methods for computing fourier transforms.[189] The mean value of the HF-HRV and LF-HRV were computed from two baseline 300 second epochs. HF and LF-HRV were natural-log transformed prior analysis to achieve a more normal distribution.[190]

Blood Samples. The biomarkers included in the biomarker project reflect the functioning of the hypothalamic-pituitary-adrenal axis, the autonomic nervous system, and various metabolic processes. The cardiovascular panel included fasting blood draws for total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. The glucose metabolism panel included fasting blood draws for insulin, glucose, and insulin-like growth factor-1. The neuroendocrine panel consisted of a 12-

Hour urine collection for characterization of cortisol, epinephrine, norepinephrine, dopamine, and creatinine.

Fasting blood samples were collected and processed according to a standardized protocol.[188] The hemoglobin A1C and cholesterol panel assays were performed at Meriter Labs using a Cobas Integra analyzer (Roche Diagnostics, Indianapolis, IN).[188] The 12-hour urine samples were collected from each participant during their overnight GCRC visit. Catecholamine assays were all performed at the May Medical Laboratory (Rochester, MN), according to a previously described, standardized protocol.[188]

Metabolic Syndrome. The presence of metabolic syndrome was ascertained according to criteria established by the National Cholesterol Education Program III (ATP III). Participants were classified as having metabolic syndrome if they met at least three of the following criteria: waist circumference >102cm for men and >88cm for women; triglycerides ≥150 mg/dL, HDL cholesterol <40 for men and <50 for women; blood pressure ≥130/85; or serum glucose ≥110 mg/dL.[44]

Sleep. Sleep was measured in the biomarker project using the PSQI. The PSQI was developed and validated by Buysee and colleagues.[160] The PSQI consists of nineteen self or bed-partner rated questions used to characterize seven components of sleep quality that include: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, use of sleep medication, and daytime dysfunction.[160] Component scores are scored ranging from 0-3. A score of 0 indicates no difficulty, while a score of 3 indicates severe difficulty. The global sleep score is a composite score of the seven component scores ranging from 0-21 with 0 score indicating no difficult and 21 indicating severe difficulty in all component areas. For the purposes of this analysis global PSQI sleep

score >5 signifies poor sleep.[160] For the purposes of this analysis only global sleep scores and subjective sleep quality measures were examined.

Covariates. Covariates were collected from the MIDUS II survey and biomarker project questionnaires. Covariates such as age, gender, education, race, marital status (single/never married, married or living with partner, widowed/divorced) and current smoking status were obtained from self-reported questionnaire data. Body mass index (BMI), regular exercise, and self-reported chronic health conditions such as heart disease, diabetes, and depression were included as they are known to be confounding influences on cardiometabolic factors, sleep quality, and HRV indices. (O'Connor et al., 2009; O'Connor & Irwin, 2010) Self-reported information regarding medications known to effect HRV, sleep, or cardiometabolic factors, were also collected to include cholesterol medications, and medications know to affect the parasympathetic nervous system (negatively: barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines; positively: cholinergic agents and β-adrenergic blocking agents).

Statistical Analysis

All analyses were performed using SAS version 9.4 (Cary, NC, USA). Descriptive statistics were evaluated using frequencies and chi-square tests for categorical variables. For continuous variables, means, and standard deviations were presented, and tests of significance were estimated using independent t-tests or Wilcoxon ranks sums test based on the normality of the variable's distribution. A confounder selection process was utilized prior to the main analyses. Covariates with a p-value ≤0.20 in bivariate analyses were added to full model for the both the generalized linear (PROC GLM) and logistic regression (PROC LOGISTIC) models. A confounder

selection process was conducted by removing covariates one at a time and those that changed the effect estimate of interest by at least 10%, or those that remained statistically significant ($p \leq 0.05$), were kept in the model. Linear regression assumptions were evaluated by examining the final model's residuals.

To evaluate the relationship between global PSQI sleep score and the individual HRV indices, a linear regression was conducted using PROC GLM with adjustment for selected confounders. This analysis was completed among all participants and then with stratification by the presence of metabolic syndrome. The GLM procedure also was used to compute adjusted least squares (LS) mean of each HRV measure among participants with good and poor sleep quality according the dichotomized global PSQI sleep score or subjective sleep quality measure. This analysis approach was repeated in separate analyses after stratification among participants with and without metabolic syndrome. Results of the analysis yielded β-coefficients and standard errors for the sleep measure of interest.

To evaluate the association between the PSQI derived sleep measures, HRV indices, and the presence of metabolic syndrome, a multivariable logistic regression was conducted using the PROC LOGISTIC procedure in SAS. To examine to what extent HRV moderates the association between sleep quality and metabolic syndrome, interaction terms were included in separate models. Interaction terms with p-values ≤ 0.20 were selected for further analysis, and subsequently dichotomized in a manner for which participants in first quartile were considered to have "low or reduced" HRV and those in other 3 quartiles were considered to have "high or normal" HRV. This process has been

used previously to categorize HRV measures.[191] The results yielded odds ratios (ORs) with 95% confidence intervals (CI).

5.4 Results

Demographic Characteristics. Among the 1,255 MIDUS II biomarker project participants, 966 had complete PSQI, metabolic syndrome, and HRV data. The study population was primarily female (55%), married (66%), and the mean (SD) age of the sample was 54±11 years. Additionally, 64% met the criteria for the presence of metabolic syndrome. Table 5.1 provides descriptive statistics for the demographic, lifestyle, and medical characteristics for the entire sample and among those with and without metabolic syndrome. Participants with and without metabolic syndrome did not differ in terms of age, marital status, cancer history, or depression. Participants differed in terms of body mass index (BMI), waist circumference, physical activity, diabetes, cholesterol medication, sex-hormone medications, and medication known to affect the parasympathetic nervous system.

Relationship between sleep and HRV. An inverse relationship was observed between PSQI sleep score and ln LF-HRV and ln SDRR among participants (n=344) with metabolic syndrome; however, there was no relationship among the entire sample (n=966) or among participants without metabolic syndrome only (n=622) (Table 5.2). Adjusted mean HRV measures stratified by PSQI sleep score or subjective sleep quality score are presented in Tables 5.3, 5.4, and 5.5. There were no differences in adjusted mean HRV measures between those with and without poor sleep based on a PSQI sleep score (>5) or subjective sleep quality (≥2) among all participants. However, among

participants with metabolic syndrome, those with good sleep characterized by PSQI sleep score (<5) had higher mean vales of ln LF-HRV relative to individuals with poor sleep.

Relationship between metabolic syndrome, sleep, and HRV. Table 5.6 presents the adjusted mean levels of HRV indices stratified by the presence of metabolic syndrome. Adjusted mean values for ln RMSSD and ln HF-HRV were higher in participants without metabolic syndrome. There were no differences in mean values for ln LF-HRV or ln SDRR between participants with and without metabolic syndrome. There were no differences in mean PSQI sleep score between participants with and without metabolic syndrome (Table 5.7). Additionally, the mean values for those with and without metabolic syndrome were both greater than 5 which meets the criteria for being a poor sleeper.[160]

Association between sleep and metabolic syndrome. Results of the multivariable association between the PSQI derived sleep and metabolic syndrome are presented in Table 5.8. Increasing PSQI sleep score (OR=1.06, 95% CI=1.01-1.11) were associated with increased odds of meeting the criteria for metabolic syndrome. Additionally, participants with poor sleep (PSQI sleep score >5) had 49% higher odds of meeting the criteria for metabolic syndrome.

Association between HRV and metabolic syndrome. Results of the multivariable association between the HRV indices and metabolic syndrome are presented in Table 5.9. Increasing Ln SDRR (OR=0.68, 95% CI=0.48-0.96) and Ln RMSSD (OR=0.77, 95% CI=0.59-0.99) were associated with lower odds of meeting the criteria for metabolic syndrome.

Relationship between sleep and metabolic syndrome, stratified by HRV. Prior to this analysis, two-way interactions between PSQI sleep score or subjective sleep quality and each HRV measure were evaluated, and interaction terms with p-values ≤0.25 were selected for further evaluation. Among participants with low HF-HRV (Quartile 1; ≤55.7) there were associations between PSQI sleep score (Poor vs. Good) and metabolic syndrome. Among participants with low LF-HRV (Quartile 1; ≤103.2) there were associations between PSQI sleep score (Poor vs Good), subjective sleep quality (Poor vs Good), and metabolic syndrome. Lastly among participants with low HRV based on SDRR (Quartile 1; ≤23.2) and RMSSD (Quartile 1; ≤103), PSQI sleep score and subjective sleep quality were associated with the presence of metabolic syndrome. Results are presented in Tables 5.10-5.13. The association were consistent although attenuated after stratifying by first the tertile vs the other two tertiles (Appendix C: Table C.2-C.5)

5.5 Discussion

Using a population-based sample of middle-aged and older adults in the United States, we reported a negative relationship between subjective sleep quality and HRV; an association between poor sleep and metabolic syndrome; and an association between low HRV and metabolic syndrome were observed after controlling for relevant covariates. These results provide further support for a relationship between disturbed sleep, autonomic imbalance, and metabolic dysregulation. Further, the strength of association between poor sleep quality and metabolic syndrome was strengthened among participants with low HRV.

Previous epidemiological studies have found that poor sleep quality, short sleep duration, and insomnia are associated with autonomic irregularities.[88,192,193] In an cross-sectional analysis of actigraphy-based measures of sleep duration and efficiency, short sleep duration, low sleep efficiency, and insomnia each were associated lower parasympathetic tone and sympathetic nervous system activation.[192] In another study, increased LF-HRV and decreased HF-HRV were observed in objectively defined insomniacs compared to healthy controls during all stages of sleep.[88]

Unlike the analysis of a multi-ethnic sample of midlife women, the current study found an association between self-reported sleep quality and metabolic syndrome; however, only modest differences in the mean values of PSQI sleep score among participants with and without metabolic syndrome were observed.[28] A population-based study of Japanese citizens (N=1481) reported elevated odds of poor sleep among those with metabolic syndrome (females OR: 2.37, 95% CI: 1.23-4.58; males: 2.71, 95% CI: 1.45-5.07).[27] In a 2012 study examining the relationship between self-reported sleep quality and metabolic syndrome and it's components among African Americans, self-reported sleep quality was not associated with metabolic syndrome nor its components.[194] In another study, sleep quality was associated with the presence of metabolic syndrome in a population of middle-aged US adults.[26] While the present study identified a cross-sectional association between sleep quality and metabolic syndrome, the magnitude of the association was not as strong in similarly designed studies.; however, this may be due to population differences. Participants of the MIDUS II biomarker project sample were older and had higher overall PSQI sleep scores relative to participants from the University of Pittsburgh's Adult and Human Behavior Project; which is not unexpected

as sleep quality worsens with age.[195] In a study of 288 twins from the Twins Heart Study, metabolic syndrome was associated with reduced HRV after controlling for covariates and genetic factors.[196] A case-control study consisting of middle-aged and older working men found that participants with metabolic syndrome had lower levels of HRV across all indices compared to healthy controls.[197]

While the current study demonstrated associations between sleep, HRV, and metabolic syndrome, it also highlighted the dynamic relationship between the parasympathetic and sympathetic nervous systems. The accumulation of metabolic syndrome components is defined by the activation of the sympathetic nervous system that subsequently leads to increased risk of cardiovascular disease; however, it is unclear as to whether the sympathetic activation precedes the develop metabolic syndrome or if it is a consequence. In a study exploring the alteration of the autonomic function in a population at-risk for metabolic syndrome, Chang and colleagues found decreased SDNN and increased LF-HRV with increasing number of metabolic components, suggesting autonomic dysfunction may be a precursor for metabolic syndrome.[198]

An advantage of this study was the large sample that included many relevant covariates. Another advantage is that we were able to consider the complex relationship between sleep quality, autonomic function, and metabolic syndrome. Additionally, all psychosocial measures and clinical assessments were derived using validated measures and standardized clinical protocols. However, there were some noteworthy limitations. In addition to being a relatively homogeneous sample (i.e., primarily white (~92%), and well-educated (~42% college grad or more), participants were required to travel to one of three research centers which may have introduced selection bias and reduced

generalizability.[188,199] Additionally, due to the cross-sectional nature of the study, it is not possible to make causal inferences regarding the pathway between sleep, autonomic function, and metabolic syndrome. Lastly, while sleep was measured using a validated measure of sleep, the PSQI, the addition of polysomnography or wrist actigraphy may have yielded different results as they are both objective measures of sleep.

In conclusion, the current investigation found that poor sleep quality was associated with lower levels of LF-HRV among participants with metabolic syndrome. Additionally, this study found that poor sleep quality and low HRV are both associated with increasing prevalence of metabolic syndrome. The significance of these results is that low HRV and poor sleep are both individually associated with increased risk for cardiovascular disease and cardiovascular disease related mortality.[200–202] Our findings highlight the protentional for interventions such heart rate variability biofeedback for increasing PNS tone and sleep quality, and to subsequently reduce the risk of cardiovascular disease and cardiovascular disease related mortality. Future studies should characterize longitudinal role of sleep and autonomic dysfunction on the development metabolic syndrome.

Table 5.1 Population characteristics with stratification by metabolic syndrome, MIDUS II study, 2004-2009

Characteristics	Overall (n=966)	Without Metabolic Syndrome (n=622)	With Metabolic Syndrome (n=344)	p-value[1]
	Mean ± SD or n (%)			
Age	54.0 ± 11.6	53.7 ± 11.9	54.5 ± 10.9	0.35
Body Mass Index (kg/m^2)	29.7 ± 6.6	27.5 ± 5.6	33.8 ± 6.3	<0.01
Waist Circumference (cm)	97.3 ± 16.2	91.5 ± 14.3	108.0 ± 13.7	<0.01
Gender				
Male	421 (43.6)	268 (43.1)	153 (44.5)	0.68
Female	545 (56.4)	354 (56.9)	191 (55.5)	
Marital Status				
Single	99 (10.3)	62 (10.0)	37 (10.8)	0.28
Married	640 (66.3)	423 (68.0)	217 (63.1)	
Divorced/Widowed/Separated	227 (23.5)	137 (22.0)	90 (26.2)	
Current Smoker				
Yes	139 (14.4)	83 (13.4)	56 (16.3)	0.22
No	826 (85.6)	538 (86.6)	288 (83.7)	
Regular physical activity at least 3 times/week				
Yes	749 (77.5)	511 (82.2)	238 (69.2)	<0.01
No	217 (22.5)	111 (17.9)	106 (30.8)	
Hypertension				
Yes	324 (33.5)	155 (24.9)	169 (49.1)	<0.01
No	642 (66.5)	467 (75.1)	175 (50.9)	
Cancer				
Yes	125 (12.9)	75 (12.1)	50 (14.5)	0.27
No	841 (87.1)	547 (87.9)	294 (85.5)	
Diabetes				
Yes	109 (11.3)	31 (5.0)	78 (22.7)	<0.01
No	857 (88.7)	591 (95.0)	266 (77.3)	
Depression				
Yes	179 (18.5)	108 (17.4)	71 (20.6)	0.21
No	787 (81.5)	514 (82.6)	273 (79.4)	
Cholesterol medication				
Yes	265 (27.4)	138 (22.2)	127 (36.9)	<0.01
No	701 (72.6)	484 (74.6)	217 (63.1)	
Sex hormone				
Yes	108 (11.2)	79 (12.7)	29 (8.4)	0.04
No	858 (88.8)	543 (87.3)	315 (91.6)	

Table 5.1 Population characteristics with stratification by metabolic syndrome, MIDUS II study, 2004-2009 (continued)

Characteristics	Overall (n=966)	Without Metabolic Syndrome (n=622)	With Metabolic Syndrome (n=344)	p-value[1]
	Mean ± SD or n (%)			
Medications that positively affect PNS activity				
Yes	138 (14.3)	67 (10.7)	71 (20.6)	<0.01
No	828 (85.7)	555 (89.2)	273 (79.4)	
Medications that negatively affect PNS activity				
Yes	178 (18.4)	103 (16.6)	75 (21.8)	0.04
No	788 (81.6)	519 (83.4)	269 (78.2)	

[1]Calculated with independent sample t-tests or Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. Abbreviations: M=Mean, SD = Standard Deviation, PNS = Parasympathetic Nervous System. Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria.

Table 5.2 Relationship between PSQI global sleep score and heart rate variability indices, MIDUS II study, 2004-2009 (n=966)

PSQI Global Sleep Score[a]	Ln HF-HRV (ms^2)[1]		Ln LF-HRV (ms^2)[2]		Ln SDRR (ms)[3]		Ln RMSSD (ms)[4]	
	B (SE)	p-value	B (SE)	p-value	B (SE)	p-value	B (SE)	p-value
All Participants (n=966)	-0.008 (0.01)	0.49	-0.014 (0.01)	0.15	-0.004 (0.004)	0.35	-0.005 (0.01)	0.39
Participants with metabolic syndrome (n=344)	-0.019 (0.02)	0.32	-0.048 (0.02)	<0.01	-0.016 (0.01)	0.02	-0.013 (0.01)	0.14
Participants without metabolic syndrome (n=622)	0.009 (0.01)	0.53	0.013 (0.01)	0.31	0.005 (0.01)	0.35	0.003 (0.01)	0.72

[1]Model adjusted for age, cholesterol medication, smoking, gender, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and marital status. [2]Model adjusted for age, cholesterol medication, hypertension, cancer, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, marital status, and waist circumference. [3]Model adjusted for age, cholesterol medication, cancer, smoking, gender, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, marital status, and waist circumference. [4]Model adjusted for age, cholesterol medication, smoking, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, marital status, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. SE= Standard Error of the mean, HF-HRV = High Frequency Heart Rate Variability (0.15-0.40 Hz), LF-HRV = Low Frequency Heart Rate Variability (0.04-0.15 Hz), SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences, β = Regression Coefficient, PSQI = Pittsburgh Sleep Quality Index, ms = Milliseconds, Ln = Natural Log, PNS = Parasympathetic Nervous System.

Table 5.3 Adjusted mean HRV measures by PSQI derived sleep measures, MIDUS II study, 2004-2009 (n=966)

HRV Measures	PSQI Global Sleep Score[a]			Sleep Quality[b]		
	Good (≤5)	Poor (>5)	p-value	Good (≥2)	Poor (<2)	p-value
Ln HF-HRV (ms^2)[1]	4.88±0.09	4.84±0.08	0.63	4.88±0.08	4.80±0.11	0.45
Ln LF-HRV (ms^2)[2]	5.24±0.08	5.17±0.08	0.34	5.19±0.07	5.21±0.10	0.88
Ln SDRR (ms)[3]	3.37±0.03	3.37±0.03	0.81	3.37±0.03	3.37±0.04	0.94
Ln RMSSD (ms)[4]	3.00±0.05	2.97±0.04	0.49	2.99±0.04	2.95±0.06	0.51

[1]Model adjusted for age, cholesterol medication, smoking, gender, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, and marital status.[2]Model adjusted for age, cholesterol medication, diabetes, hypertension, gender, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, marital status, and waist circumference. [3]Model adjusted for age, cholesterol medication, cancer, hypertension, smoking, gender, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, and waist circumference.[4]Model adjusted for age, cholesterol medication, smoking, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) and positively affect PNS activity, marital status, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). Abbreviations: SE= Standard Error, HF-HRV = High Frequency-heart rate variability, LF-HRV = Low Frequency-heart rate variability, SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences, β = Regression Coefficient, PSQI = Pittsburgh Sleep Quality Index, ms = Milliseconds, Ln = Natural Log PNS = Parasympathetic Nervous System.

Table 5.4 Adjusted mean HRV measures by PSQI derived sleep measures, among participants with metabolic syndrome, MIDUS II study, 2004-2009 (n=344)

Mean HRV Measures	PSQI Global Sleep Score[a]			Sleep Quality[b]		
	Good (≤5)	Poor (>5)	p-value	Good (<2)	Poor (≥2)	p-value
Ln HF-HRV (ms^2)[1]	4.89±0.15	4.75±0.13	0.33	4.86±0.12	4.64±0.16	0.18
Ln LF-HRV (ms^2)[2]	5.30±0.12	5.05±0.11	0.04	5.20±0.09	4.94±0.13	0.06
Ln SDRR (ms)[3]	3.30±0.05	3.24±0.05	0.22	3.30±0.05	3.19±0.06	0.06
Ln RMSSD (ms)[4]	2.99±0.08	2.91±0.07	0.27	2.99±0.06	2.86±0.08	0.12

[1]Model adjusted for age, cholesterol medication, smoking, gender, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and Phenothiazines) affect PNS activity, and marital status. [2]Model adjusted for age, cholesterol medication, diabetes, hypertension, gender, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, marital status, and waist circumference. [3]Model adjusted for age, cholesterol medication, cancer, hypertension, smoking, gender, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) affect PNS activity, and waist circumference.[4]Model adjusted for age, cholesterol medication, smoking, medications that negatively (barbiturates, benzodiazepines, antidepressants, antipsychotics, and phenothiazines) and positively (cholinergic agents and β-adrenergic blocking agents) affect PNS activity, marital status, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). Abbreviations: SE= Standard Error, HF-HRV = High Frequency-heart rate variability, LF-HRV = Low Frequency-heart rate variability, SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences, β = Regression Coefficient, PSQI = Pittsburgh Sleep Quality Index, ms = Milliseconds, Ln = Natural Log PNS = Parasympathetic Nervous System.

Table 5.5 Adjusted mean HRV measures by PSQI derived sleep measures among participants without metabolic syndrome, MIDUS II Study, 2004-2009 (n=622)

Mean HRV Measures	PSQI Global Sleep Score[a]			Sleep Quality[b]		
	Good (≤5)	Poor (>5)	p-value	Good (<2)	Poor (≥2)	p-value
Ln HF-HRV (ms^2)[1]	4.91±0.12	4.95±0.11	0.65	4.92±0.09	4.95±0.13	0.79
Ln LF-HRV (ms^2)[2]	5.04±0.12	5.10±0.12	0.53	5.09±0.10	5.25±0.13	0.14
Ln SDRR (ms)[3]	3.44±0.05	3.47±0.04	0.40	3.45±0.04	3.51±0.05	0.16
Ln RMSSD (ms)[4]	3.02± 0.07	3.04±0.06	0.78	3.05±0.05	3.06±0.07	0.83

[1]Model adjusted for age, cholesterol medication, smoking, gender, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and marital status. [2]Model adjusted for age, cholesterol medication, diabetes, hypertension, gender, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, marital status, and waist circumference. [3]Model adjusted for age, cholesterol medication, cancer, hypertension, smoking, gender, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference.[4]Model adjusted for age, cholesterol medication, smoking, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) and positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, marital status, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). Abbreviations: SE= Standard Error, HF-HRV = High Frequency-heart rate variability, LF-HRV = Low Frequency-heart rate variability, SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences, β = Regression Coefficient, PSQI = Pittsburgh Sleep Quality Index, ms = Milliseconds, Ln = Natural Log PNS = Parasympathetic Nervous System.

Table 5.6 Mean HRV measures by metabolic syndrome, MIDUS II Study, 2004-2009 (n=966)

Mean HRV Measures	Metabolic Syndrome[a]		
	Yes	No	p-value
Ln HF-HRV (ms^2)[1]	4.86±0.09	5.03±0.09	0.05
Ln LF-HRV (ms^2)[2]	5.04±0.08	5.16±0.08	0.16
Ln SDRR (ms)[3]	3.34±0.04	3.40±0.03	0.08
Ln RMSSD (ms)[4]	2.92± 0.05	3.03±0.05	0.01

[1]Model adjusted for age, cholesterol medication, smoke, gender, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) and positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and marital status. [2]Model adjusted for age, cholesterol medication, diabetes, gender medications negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) and positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [3]Model adjusted for age, cholesterol medication, cancer, hypertension, smoke, gender, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference.
[4]Model adjusted for age, cholesterol medication, smoking, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) and positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and marital status. [a]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. Abbreviations: SE= Standard Error, HF-HRV = High Frequency-heart rate variability, LF-HRV = Low Frequency-heart rate variability, SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences, β = Regression Coefficient, PSQI = Pittsburgh Sleep Quality Index, MS = Milliseconds, Ln = natural log PNS = Parasympathetic Nervous System.

Table 5.7 Comparison of PSQI derived sleep measures by metabolic syndrome, MIDUS II Study, 2004-2009 (n=966)

Sleep Measure	Metabolic Syndrome[b]		
	Yes	No	p-value
	Mean ± SE	Mean ± SE	0.07
PSQI Global Sleep Score[a,1]	7.90 ± 0.25	7.44±0.24	
Subjective Sleep Quality[2]	%	%	0.05
Good (<2)	78	84	
Poor (≥2)	22	16	

[1]Model adjusted for age, hypertension, smoking, gender, medications that negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, exercise, and marital status. [2]Model two adjusted for age, depression, tobacco use, and gender. [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. Abbreviations: PNS = Parasympathetic Nervous System.

Table 5.8 Odds of metabolic syndrome by PSQI derived sleep measures, MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[a]	
	OR (95% CI)	p-value
PSQI Global Score[1](Continuous)	1.06 (1.01-1.11)	<0.01
PSQI Global Score[2]		
Good (≤5)	Reference	0.02
Poor (>5)	1.49 (1.07-2.08)	
Sleep Quality[3]		
Good (<2)	Reference	0.12
Poor (≥2)	1.37 (0.92-2.06)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively affect PNS activity, and waist circumference. [a]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, PNS = Parasympathetic Nervous System.

Table 5.9 Odds of metabolic syndrome by HRV measures, MIDUS II Study, 2004-2009 (n=966)

HRV Measures	Metabolic Syndrome[a]	
	OR (95% CI)	p-value
Ln HF-HRV (ms^2)[1]	0.90 (0.79-1.02)	0.08
Ln LF-HRV (ms^2)[2]	0.87 (0.76-1.01)	0.07
Ln SDRR (ms)[3]	0.68 (0.48-0.96)	0.03
Ln RMSSD (ms)[4]	0.77 (0.59-0.99)	0.04

[1]Model adjusted for age, cholesterol medication, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [2]Model adjusted for age, cholesterol medication, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference.[3]Model adjusted for age, cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [4]Model adjusted for age, cholesterol medication, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, HF-HRV = High Frequency-heart rate variability, LF-HRV = Low Frequency-heart rate variability, SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table 5.10 Multivariable associations among PSQI derived sleep measures and Metabolic Syndrome, stratified by HF-HRV. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	HF-HRV (Quartile 1) (≤55.7)[c] (n=242)		HF-HRV (Quartile 2-4) (>55.7)[c] (n=724)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.07 (0.99-1.16)	0.10	1.06 (1.00-1.11)	0.05
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	0.04	Reference	0.14
Poor (>5)	1.93 (1.02-3.64)		1.35 (0.91-2.01)	
Sleep Quality[3,b]				
Good (<2)	Reference	0.32	Reference	0.23
Poor (≥2)	1.45 (0.69 -3.14)		1.34 (0.83-2.17)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, HF-HRV = High Frequency-heart rate variability, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table 5.11 Multivariable associations among PSQI derived sleep measures and metabolic syndrome, stratified by LF-HRV. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	LF-HRV Quartile 1 (≤103.2)[c] (n=245)		LF-HRV Quartile 2-4 (>103.2)[c] (n=721)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.10 (1.01-1.20)	0.03	1.04 (0.99-1.10)	0.12
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	0.04	Reference	0.18
Poor (>5)	2.00 (1.05-3.80)		1.31 (0.89-1.95)	
Sleep Quality[3,b]				
Good (<2)	Reference	0.01	Reference	0.77
Poor (≥2)	2.88 (1.23-6.72)		1.07 (0.67-1.73)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, LF-HRV = Low Frequency-heart rate variability, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table 5.12 Multivariable associations among PSQI derived sleep measures and metabolic syndrome, stratified by SDRR. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	SDRR Quartile 1 (≤23.21)[c] (n=239)		SDRR Quartile 2-4 (>23.21)[c] (n=727)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.17 (1.06-1.28)	<0.01	1.03 (0.97-1.08)	0.34
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	<0.01	Reference	0.36
Poor (>5)	2.78 (1.40-5.54)		1.20 (0.82-1.77)	
Sleep Quality[3,b]				
Good (<2)	Reference	<0.01	Reference	0.91
Poor (≥2)	3.29 (1.38-7.86)		1.03 (0.64-1.65)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, SDRR = Standard Deviation of R-R Intervals, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table 5.13 Multivariable associations among PSQI derived sleep measures and metabolic syndrome, stratified by RMSSD. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	RMSSD Quartile 2-4 (<103) [c] (n=241)		RMSSD Quartile 2-4 (≥103) [c] (n=725)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.11 (1.02-1.21)	0.01	1.04 (0.99-1.09)	0.16
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	0.02	Reference	0.20
Poor (>5)	2.18 (1.14-4.20)		1.29 (0.87-1.92)	
Sleep Quality[3,b]				
Good (<2)	Reference	0.09	Reference	0.56
Poor (≥2)	1.98 (0.91-4.33)		1.15 (0.71-1.87)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV.

Abbreviations: OR=Odds Ratio, CI= Confidence Interval, RMSSD = Root Mean Square of Successive Differences, MS = Milliseconds, PNS = Parasympathetic Nervous System.

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APPENDIX A: SUPPLEMENTARY TABLES AND FIGURE FOR CHAPTER 3

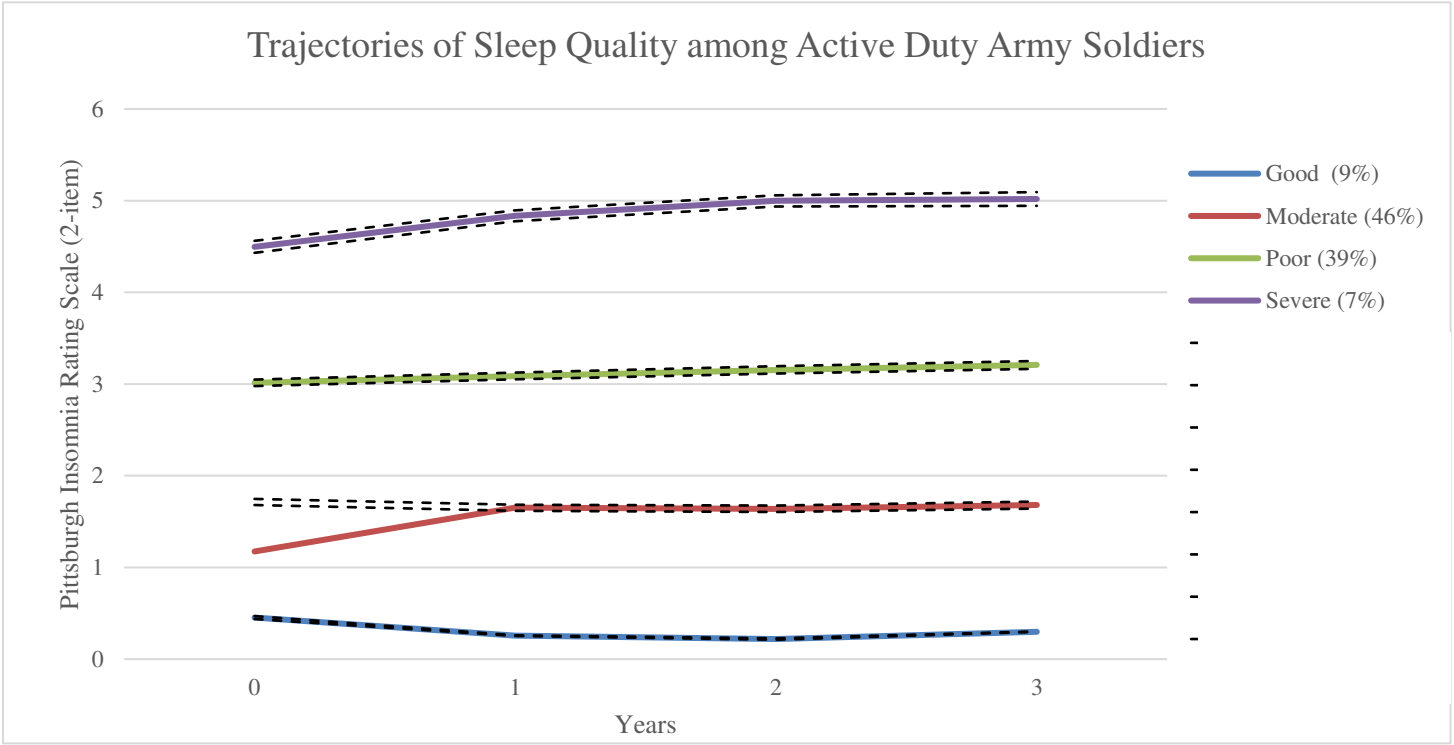


Figure A.1 Latent group trajectories for PIRS-2 sleep measures over 3 years obtained with repeated measures latent class analysis (n=127,348). Only participants who have completed 3 GAT 2.0 Surveys from December 31, 2013 – August 31, 2017 were included. A cut-off score of 2 was 88% specific and 96% specific for determining the presence of insomnia.[1]

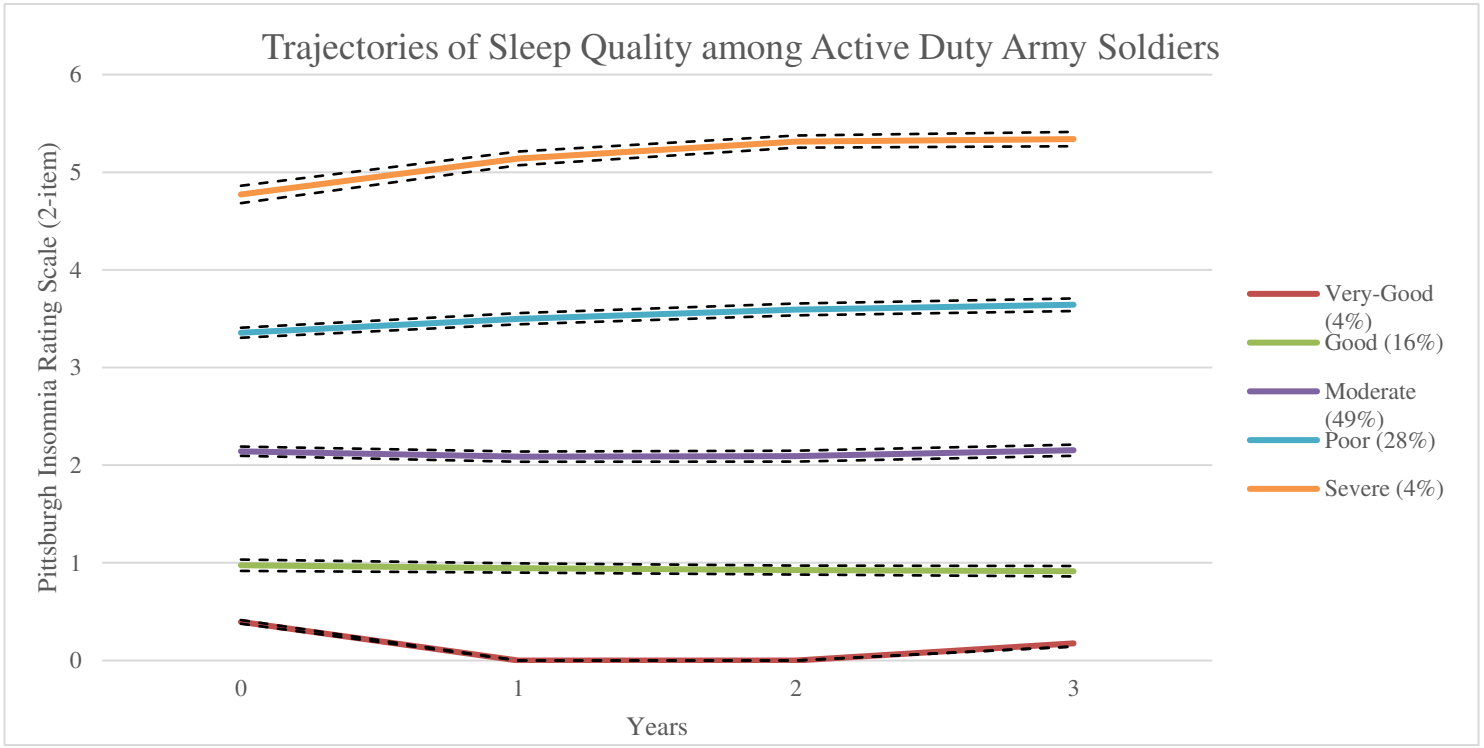


Figure A.2 Latent group trajectories for PIRS-2 sleep measures over 3 years obtained with repeated measures latent class analysis (n=127,348). Only participants who have completed 3 GAT 2.0 Surveys from December 31, 2013 – August 31, 2017 were included. A cut-off score of 2 was 88% specific and 96% specific for determining the presence of insomnia.[1]

Table A.1 Resiliency Measures by Military Occupation Category (n=127,348)

Variables	Combat MOS (n=186)	Non-Combat MOS (n=56)	p-value
	Mean ± SE	Mean ± SE	
Total Fitness	4.05 ±0.01	4.05±0.01	0.52
Emotional Fitness	3.88 ±0.01	3.90 ±0.01	<0.01
Social Fitness	4.03 ± 0.01	4.00 ± 0.01	<0.01
Family Fitness	4.09 ± 0.02	4.10 ± 0.02	<0.01
Spiritual Fitness	4.23 ± 0.02	4.24 ± 0.02	<0.01
Each model adjusted for age, gender, race, marital status, education, rank, alcohol use, physical activity, sleep medication, and diet. Abbreviations: SE = Standard Error, MOS= Military Occupation Specialty. [a]Higher scores represent more emotional, social, family, and spiritual fitness.			

APPENDIX B: SUPPLEMENTARY TABLES AND FIGURES FOR CHAPTER 4

Table B.1 Fit statistics for latent class models

Number of Classes	Residual df	AIC	BIC	G^2	Entropy	BS-LRT	%Solution
2	**6**	**26.56**	**57.96**	**8.56**	**0.69**	**--**	**100.00%**
3	1	30.20	79.05	2.20	0.69	0.22	63.00%
4	-4	38.75	105.04	0.75	0.64	0.39	10.60%
5	-9	48.59	132.33	0.59	0.70	--	88.6%

Abbreviations: df = degrees of freedom; AIC = Akaike Information Criterion; BIC= Bayesian Information Criterion; BS-LRT – Bootstrap Likelihood Ratio Test; %Solution – Percentage of seeds associated with best fitted model. Bold indicated the selected model.

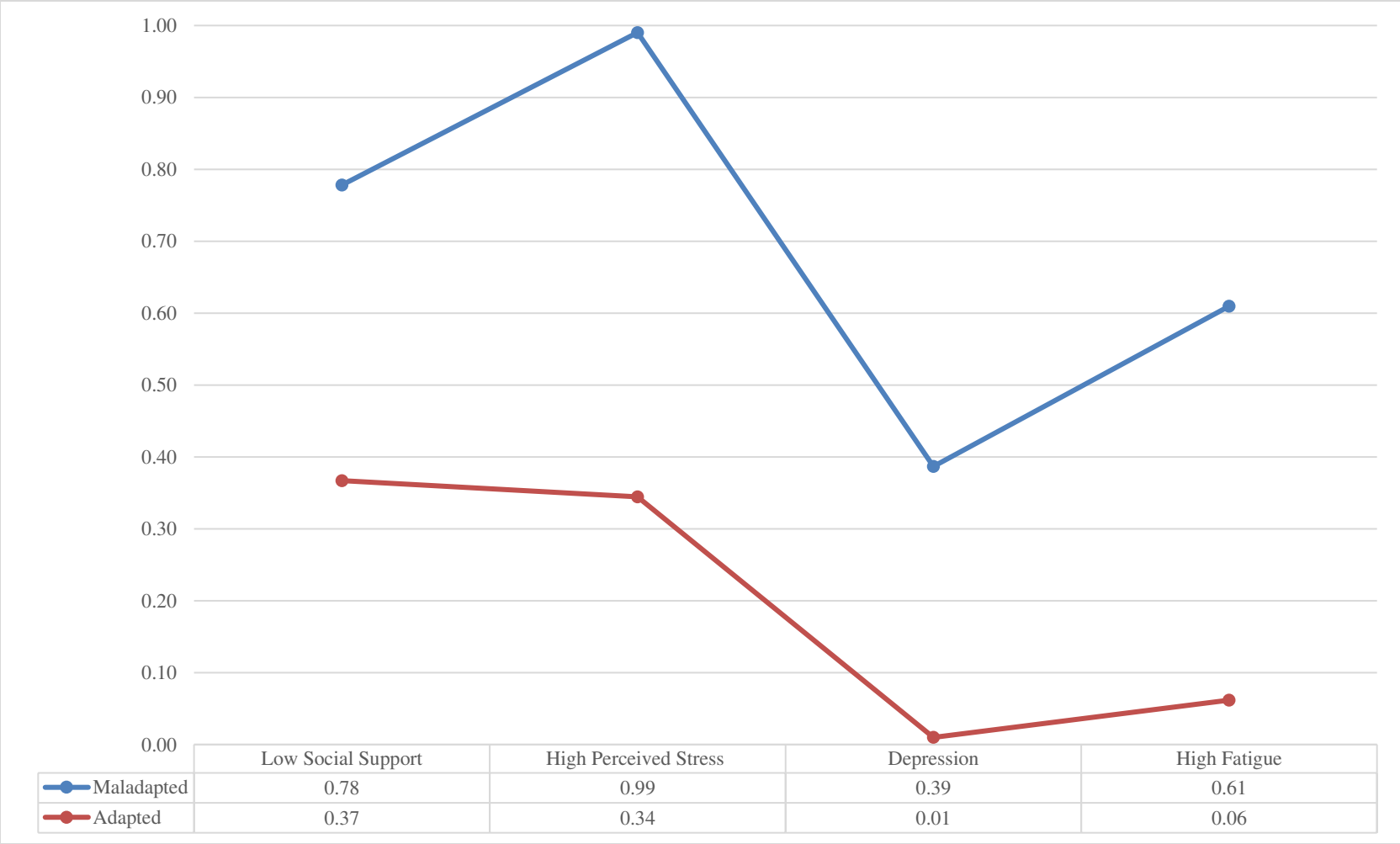
Table B.2 Prevalence of latent class membership and item-response probabilities among police officers, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

Latent Class Characteristics	Latent Class Membership	
	Shiftwork Maladapted (n=56)	Shiftwork Adapted (n=186)
Probability of class membership	.29	.71
Conditional probability of a maladapted response		
Low Social Support[1]	.78	.37
High Perceived Stress[2]	.99	.34
Depression[3]	.39	.001
High Fatigue[4]	.61	.006

[1]Indicator variable was derived from the Social Provision Scale. Officers with score below the sample median are considered to have low social support. [2]Indicator variable was derived from the Perceived Stress Scale. Officers in the highest quartile are considered to have high perceived stress. [3]Indicator variable was derived from the Center for Epidemiologic Studies Depression Scale (CESD). Officer with score > 16 are considered to have depression. [4]Indicator variable were derived from the Vital Exhaustion scale. Officers in highest quartile are considered to have high fatigue.

Table B.3 Description of latent class analysis indicator variables

Low Social Support	Social support is measured using the Social Provisions Scale which consists of 22 items that were developed to assess six provisions of social relationship.[203] For the purposes of this analysis participants below the sample median are considered to have low social support.
High Perceived Stress	Perceived stress is measured using the perceived stress scale, which is a 14-item scale that measures the frequency of stressful events and experiences during the previous month.[162] Perceived stress is measured on a 5-point Likert scale ranging from 0-4. For this analysis participants in the highest quartile are considered to have high perceived stress.
Depression	Depression was measured using the center for epidemiologic studies depression scale.[204] Participants with a score ≥16 are considered to have depression.
High Fatigue	Fatigue was measured using vital exhaustion which measures: feelings of excessive fatigue and lack of energy; increasing irritability; and feelings of demoralization.[163] For the purposes of this analysis Participants in the highest quartile are considered to have high fatigue.



	Low Social Support	High Perceived Stress	Depression	High Fatigue
Maladapted	0.78	0.99	0.39	0.61
Adapted	0.37	0.34	0.01	0.06

Figure B.1 Prevalence of latent class membership and latent indicator variable probabilities among police officers, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

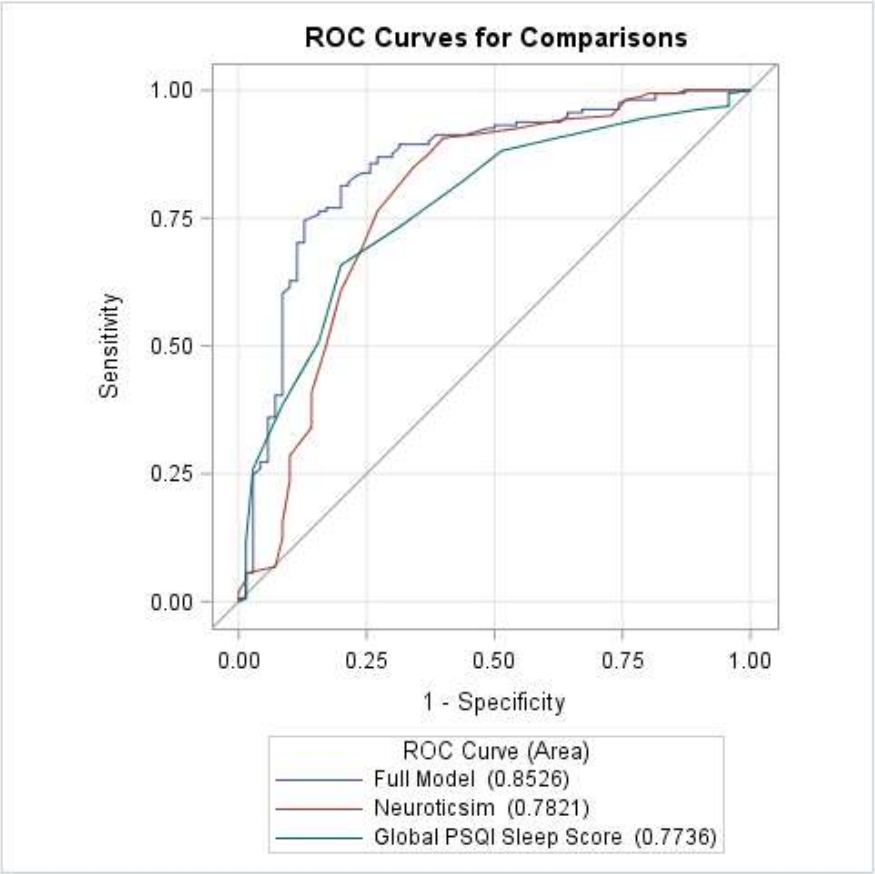


Figure B.2 Receiver operating characteristic curves for membership to shiftwork adapted latent subgroup. Full model area under the curve = 0.85; 95% confidence interval: 0.79-0.91; Neuroticism area under the curve = 0.78; 95% confidence interval: 0.71-0.86; Global PSQI sleep score area under the curve = 0.77; 95% confidence interval: 0.71-0.84

Table B.4 Individual predictors of shiftwork adaptation, BCOPS study, 2004-2009 (n=242)

Variables	Adapted (n=186)	Maladapted (n=56)	p-value
	%	%	
Age			
<40 years	51.2	55.4	0.57
≥40 years	48.9	44.6	
Race			
White	82.7	88.7	0.30
Non-White	17.30	11.3	
Sex			
Male	89.8	75.0	<0.01
Female	10.2	25.0	
Marital Status			
Single	8.7*	19.6	0.05
Married	78.3	62.5	
Divorced	13.0	17.9	
Income			
<$70,000	22.4	25.0	0.50
$70,000 – $90,000	31.3	37.5	
$90,000+	46.4	37.5	
Education			
<=12 Years	11.4	8.9	0.88
College < 4 Years	52.4	53.6	
College 4+ Years	36.2	36.2	
Tobacco Use			
Never	54.4	48.2	0.27
Former	17.4	12.5	
Current	28.3	39.3	

Table B.4 Individual predictors of shiftwork adaptation, BCOPS study, 2004-2009 (n=242) (continued)

Variables	Adapted (n=186)	Maladapted (n=56)	p-value
	%	%	
Servings of food cooked in fat per day			
High	73.7	89.3	0.02
Low	26.3	10.7	
Servings of vegetables per day			
High	67.7	51.8	0.03
Low	32.3	48.2	
Servings of fruit per day			
High	88.7	73.3	<0.01
Low	11.3	26.8	
PSQI Subjective Sleep Quality			
Poor	30.8	73.2	<0.01
Good	69.2	26.8	
Each predictor was run as a separate bivariate model.			

Table B.4 Individual predictors of shiftwork adaptation, BCOPS study, 2004-2009 (n=242) (continued)

Variables	Adapted (n=186)	Maladapted (n=56)	p-value
	Mean ± SD	Mean ± SD	
Age, Years	40.3 ± 7.3	39.3 ± 6.1	0.35
Neuroticism	12.6 ± 5.2	21.0 ± 7.5	<0.01
Extraversion	30.0 ± 5.4	26.3 ± 6.6	<0.01
Openness	23.4 ± 5.3	23.4 ± 4.8	0.98
Agreeableness	31.6 ± 4.8	28.3 ± 5.6	<0.01
Conscientiousness	33.8 ± 5.6	29.7 ± 7.2	<0.01
Hardiness	28.9 ± 4.5	24.8 ± 5.5	<0.01
Conflict	2.4 ± 2.0	3.1 ± 2.2	0.03
Independence	6.4 ± 1.14	3.1 ± 2.2	0.05
Active-Recreational Orientation	6.1 ± 1.9	5.3 ± 2.2	0.01
Organization	6.6 ± 2.0	4.9 ± 2.	<0.01
Control	5.1 ± 1.9	5.0 ± 2.2	0.64
Number of Children	2.6± 1.2	2.9± 1.5	0.18
PSQI- Global Sleep Score	5.9± 2.9	5.0± 2.2	<0.01

Abbreviations: SD = Standard Deviation, FES = Family Environment Scale, PSQI = Pittsburgh Sleep Quality Index. [a]Higher scores represent more extraversion, agreeableness, openness, conscientiousness, or hardiness. [b]Higher scores correspond to more family independence, active-recreational orientation, conflict, control, or organization. Each predictor was run as a separate bivariate model.

Table B.5 Multivariable predictors of shiftwork adaptation, BCOP Study, 2004-2009 (n=241)

Predictors	OR (95% CI)	p-value
Neuroticism	0.85 (0.80-0.90)	<0.01
PSQI-Global Sleep Score	0.74 (0.65-0.84)	<0.01
Abbreviations: OR = Odds Ratio; CI = Confidence Interval; PSQI = Pittsburgh Sleep Quality Inventory.		

Table B.6 Mean (Standard Error) levels for inflammatory measures by latent class membership, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

Inflammatory Measures	Latent Class Membership		Day shift (n=188)	p-value[a]
	Adapted (n=186)	Maladapted (n=56)		
Ln C-Reactive Protein (mg/L)	0.74±0.10	0.68±0.14	0.57±0.09	0.36
Ln Interleukin-6 (pg/mL)	0.66±0.05	0.67±0.08	0.45±0.05*	0.01
Tumor Necrosis Factor-A (mg/mL)	4.81±0.18*	5.60±0.28	5.00±0.15*	0.03
Fibrinogen (mg/dL)	324.85±6.87	319.81±10.39	318.17±6.29	0.69
[1]Model adjusted for age, gender, BMI, and marital status. [2]Model adjusted for age, gender, BMI, and alcohol. [3]Model adjusted for gender, race, BMI, and tobacco. [4]Model adjusted for age, race, BMI, and marital status. [a]Overall p-value for variable of interest. *p≤0.05 versus maladapted group. Abbreviations: SE= Standard Error, Ln = Natural Log.				

Table B.7 Mean (Standard Error) levels for HRV measures by latent class membership, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

HRV Indices	Latent Class Membership		Day shift (n=188)	p-value[a]
	Adapted (n=186)	Maladapted (n=56)		
Ln SDNN (ms)	3.30±0.04	3.30±0.06	3.28±0.04	0.87
Ln RMSSD (ms)	3.65±0.06	3.64±0.08	3.56±0.06	0.39
Ln HF-HRV (ms^2)	4.85±0.09	5.01±0.15	4.96±0.10	0.58
Ln LF-HRV (ms^2)	5.30±0.07	5.28±0.12	5.30±0.08	0.99

[1]Model adjusted for age, physical activity, BMI, and antidepressants. [2]Model adjusted for age, physical activity, BMI, and antidepressants. [3]Model adjusted for age, gender, physical activity, and antidepressants. [4]Model adjusted for age, gender, physical activity, and BMI. [a]Overall p-value for variable of interest. *p<0.05 versus maladapted group. Abbreviations: SE= Standard Error, Ln = Natural Log, HF-HRV = High Frequency Heart Rate Variability (0.15-0.40 Hz), LF-HRV = Low Frequency Heart Rate Variability (0.04-0.15 Hz), SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences

Table B.8 Mean (Standard Error) cardiometabolic measures by latent class membership, BCOPS study, Buffalo, NY, USA, 2004-2005 (n=242)

Cardiometabolic Measures	Latent Class Membership		Day shift (n=188)	p-value[a]
	Adapted (n=186)	Maladapted (n=56)		
High Density lipoprotein (mg/dL)[1]	51.03±1.24	48.067±1.81	50.06±1.11	0.32
Low density protein (mg/dL)[2]	127.38±2.76	128.71±4.79	123.12±2.55	0.37
Ln Triglycerides (mg/dL)[3]	4.40±0.06	4.56±0.09	4.45±0.05	0.21
Glucose (mg/mL)[4]	90.09±1.04	92.81±1.56	90.71±0.91	0.25
Systolic Blood Pressure[5]	122.87±1.00	123.67±1.70	120.98±0.92	0.24
Diastolic Blood Pressure[6]	77.73±0.99	80.16±1.41	77.61±0.87	0.22
Waist Circumference[7]	91.69±1.41	88.83±1.75	91.22±1.34	0.27
HbA1C, %[8]	5.59±0.04	5.60±0.07	5.65±0.04	0.47
Ln Insulin (uu/mL)[9]	1.83±0.07*	2.04±0.10	1.90±0.07	0.10
Adiponectin (ng/mL)[10]	14187.90±644.10	13422.79±928.90	14006.41±548.90	0.73
Ln Leptin (pg/mL)[11]	9.37±0.07	9.53±0.10	9.40±0.06	0.35
Metabolic Syndrome Components[12]	1.40±0.12	1.66±0.158	1.56±0.11	0.20

[1]Model adjusted for gender, alcohol, physical activity, BMI, and marital status. [2]Model adjusted for race, physical activity, and BMI. [3]Model adjusted for gender, race, and BMI. [4]Model adjusted for age, gender, BMI, and education. [5]Model adjusted for age, race, alcohol, and BMI. [6]Model adjusted for age, gender, BMI, and marital status. [7]Model adjusted for age, gender, alcohol, antidepressants, tobacco, and marital status. [8]Model adjusted for age, race, and BMI. [9]Model adjusted for gender, BMI, and antidepressants. [10]Model adjusted for age, gender, race, BMI, and marital status. [11]Model adjusted for gender, race, BMI, and tobacco. [12]Model adjusted for gender, BMI, and antidepressants. [a]Overall p-value for variable of interest. *p≤0.05 versus maladapted group. Abbreviations: SE= Standard Error, Ln = Natural Log.

APPENDIX C: SUPPLEMENTARY TABLES FOR CHAPTER 5

Table C.1 Interaction terms for the association between PSQI derived sleep score and HRV indices and metabolic syndrome, MIDUS II Study, 2004-2009 (n=966)

HRV Measures	Metabolic Syndrome[a]	
	Estimate	p-value
PSQI Global Sleep Score[a] * Ln HF-HRV (ms^2)[1]	-0.0001	0.11
PSQI Global Sleep Score[a] * Ln LF-HRV (ms^2)[2]	-0.0002	0.01
PSQI Global Sleep Score[a] * Ln SDRR (ms)[3]	-0.004	0.06
PSQI Global Sleep Score[a] * Ln RMSSD (ms)[4]	-0.003	0.05
PSQI Global Sleep Score * Ln HF-HRV (ms^2)[1]	-0.0003	0.03
PSQI Global Sleep Score * Ln LF-HRV (ms^2)[2]	-0.0004	0.01
PSQI Global Sleep Score * Ln SDRR (ms)[3]	-0.01	0.01
PSQI Global Sleep Score * Ln RMSSD (ms)[4]	-0.01	<0.01
Sleep Quality * Ln HF-HRV (ms^2)[1]	-0.0003	0.23
Sleep Quality * Ln LF-HRV (ms^2)[2]	-0.001	0.03
Sleep Quality * Ln SDRR (ms)[3]	-0.02	0.01
Sleep Quality * Ln RMSSD (ms)[4]	-0.01	0.10

[1]Model adjusted for age, cholesterol medication, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [2]Model adjusted for age, cholesterol medication, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and

waist circumference [3]Model adjusted for age, cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [4]Model adjusted for age, cholesterol medication, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [a] Analyzed as a continuous variable. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, HF-HRV = High Frequency-heart rate variability, LF-HRV = Low Frequency-heart rate variability, SDRR = Standard Deviation of R-R Intervals, RMSSD = Root Mean Square of Successive Differences, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table C.2 Multivariable associations among PSQI derived sleep measures and metabolic syndrome, stratified by HF-HRV. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	HF-HRV (Tertile 1) (≤74.8)[c] (n=384)		HF-HRV (Tertile 2-3) (>74.8)[c] (n=768)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.09 (1.01-1.17)	0.02	1.04 (0.98-1.10)	0.18
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	0.02	Reference	0.25
Poor (>5)	1.98 (1.13-3.49)		1.28 (0.84-1.95)	
Sleep Quality[3,b]				
Good (<2)	Reference	0.13	Reference	0.53
Poor (≥2)	1.69 (0.86-3.33)		1.18 (0.70-1.98)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, HF-HRV = High Frequency-heart rate variability, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table C.3 Multivariable associations among PSQI derived sleep measures and metabolic syndrome, stratified by LF-HRV. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	LF-HRV Terile 1 (≤137.7)[c] (n=384)		LF-HRV Tertile 2-3 (>137.7)[c] (n=768)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.10 (1.02-1.18)	0.02	1.04 (0.99-1.10)	0.14
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	0.01	Reference	0.29
Poor (>5)	2.15 (1.22-3.78)		1.26 (0.82-1.92)	
Sleep Quality[3,b]				
Good (<2)	Reference	0.02	Reference	0.75
Poor (≥2)	2.27 (1.11-4.63)		1.09 (0.67-1.80)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, LF-HRV = Low Frequency-heart rate variability, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table C.4 Multivariable associations among PSQI derived sleep measures and metabolic syndrome, stratified by SDRR. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	SDRR Tertile 1 (≤25.8)[c] (n=384)		SDRR Tertile 2-3 (>25.8)[c] (n=768)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.12 (1.04-1.21)	<0.01	1.03 (0.97-1.08)	0.39
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	0.01	Reference	0.45
Poor (>5)	2.24 (1.27-3.97)		1.17 (0.41-1.04)	
Sleep Quality[3,b]				
Good (<2)	Reference	0.02	Reference	0.90
Poor (≥2)	2.43 (1.18-5.03)		1.03 (0.63-1.71)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [a]Higher PSQI global sleep scores indicate poorer sleep quality with a range of 0-21. [b]Subjective sleep quality is measured using a 4-point Likert scale ranging from 0-3 ("Very good" to "Very bad"). [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, SDRR = Standard Deviation of R-R Intervals, MS = Milliseconds, PNS = Parasympathetic Nervous System.

Table C.5 Multivariable associations among PSQI derived sleep measures and metabolic syndrome, stratified by RMSSD. MIDUS II Study, 2004-2009 (n=966)

Sleep Measures	Metabolic Syndrome[b]			
	RMSSD Tertile 1 (≤13.8)[c] (n=384)		RMSSD Tertile 2-3 (>13.8)[c] (n=768)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
PSQI Global Sleep Score (Continuous)[1,a]	1.09 (1.01-1.17)	0.02	1.04 (0.99-1.11)	0.15
PSQI Global Sleep Score[2,a]				
Good (≤5)	Reference	0.02	Reference	0.24
Poor (>5)	1.97 (1.13-3.43)		1.29 (0.84-1.97)	
Sleep Quality[3,b]				
Good (<2)	Reference	0.14	Reference	0.46
Poor (≥2)	1.64 (0.85-3.18)		1.21 (0.72-2.04)	

[1]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [2]Model adjusted for cholesterol medication, depression, smoking, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) and negatively (Barbiturates, Benzodiazepines, Antidepressants, Antipsychotics, and Phenothiazines) affect PNS activity, and waist circumference. [3]Model adjusted for cholesterol medication, gender, medications that positively (Cholinergic Agents and β-adrenergic blocking agents) affect PNS activity, and waist circumference. [b]Metabolic Syndrome is defined according to the National Cholesterol Education Program Expert Panel criteria. [c]For this analysis participants in the lowest quartile are considered to have reduced HRV; whereas, the remaining three quartiles are considered to have nonreduced HRV. Abbreviations: OR=Odds Ratio, CI= Confidence Interval, RMSSD = Root Mean Square of Successive Differences, MS = Milliseconds, PNS = Parasympathetic Nervous System.