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Relationships Of Chronotype, Social Jetlag, Sleep, Physical Activity And Diet With Mood, Perceived Stress, Obesity, Blood Pressure And Prostate Cancer

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RELATIONSHIPS OF CHRONOTYPE, SOCIAL JETLAG, SLEEP, PHYSICAL ACTIVITY AND DIET WITH MOOD, PERCEIVED STRESS, OBESITY, BLOOD PRESSURE AND PROSTATE CANCER

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ABSTRACT

Background: Chronotype, social jetlag, poor sleep, proinflammatory diet, and low physical activity have been associated with increased risk of chronic diseases: obesity, diabetes, cardiovascular disease, depression and cancer. Yet the relationships between these factors have not been extensively investigated in prospective studies.

Methods: Two studies were conducted. ***The first study*** followed 390 healthy men and women ages 21-35 for two years. Social jetlag [SJL] and sleep measures (total sleep time [TST], sleep onset latency [SOL], wake after sleep onset [WASO]), sleep efficiency [SE]), were derived from physical activity personal (armband) monitoring. The participants wore the armband for 4-10 days at 6-month intervals (1,431 observations). Temporal consistency of repeated sleep measures was analyzed using generalized linear mixed models (GLMM). Repeated measures latent class analyses (RMLCA) identified subgroups among participants with adequate or inadequate sleep characteristics over time. Relationships between chronotype, absolute SJL, sleep measures and anthropometric measures (Body Mass Index [BMI], Percent Body Fat [%BF], Waist-to-Hip Ratio [WHR], Waist-to-Height Ratio [WHtR], Systolic Blood Pressure [SBP] and Diastolic Blood Pressure [DBP], Total Mood Disturbance score [TMD], and Perceived Stress Score [PSS]) were analyzed using GLMM for repeated measures. Stratification by latent chronotype group was used to study effect modification.

The second study examined association between energy-density Dietary Inflammatory Index (e-DII) and incident PrCA among 40,161 men ages 45-69 at recruitment

(2002-2003) and followed for a mean of 9.7 years. The e-DII was calculated from a food frequency questionnaire (FFQ) at baseline and categorized into quartiles. Incident PrCA cases were ascertained via linkage with cancer registry and categorized into three groups: high-risk, intermediate and low-risk. Accelerated failure time models were fit to model time-to-development of incident PrCA. Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) of high- and intermediate risk PrCA. In all analyses, the lowest quartile of e-DII representing a more anti-inflammatory diet was used as the referent group.

Results: Minor temporary changes were observed only for SJL, chronotype and TST. The RMLCA identified two groups of absolute SJL: low (mean±SE: 0.8±0.6 h, 58%) and high (1.4±0.8, 42%); the latter were employed and had an evening chronotype. Subgroups with disrupted sleep tended to be male, African American, have a lower income, and an evening chronotype relative to those with normal sleep. Chronotype and absolute SJL were not associated with anthropometric characteristics. TST <6 h, SE <85% or WASO ≥60 min increased odds of high %BF, WHR or WHtR in participants with early chronotypes. Those with early chronotypes and sleep latency ≥12 min had 1.9 times increased odds of high SBP (95%CI: 1.15-3.16, $p_{interaction}$=0.02). Among late chronotypes, TST <6 hours was associated with 2.6 times increased odds of high SBP (95%CI: 1.08-6.40, $p_{interaction}$=0.74).

Time-to-development of incident total PrCA did not differ by quartile of e-DII; although, among Whites, it was shorter relative to other races ($AF_{Q4\ vs.Q1}$=1.16; 95%CI:1.01-1.34). The hazard Ratio (HR) for high-risk PrCA was increased by 36% in the third quartile of the e-DII (95%CI:1.04-1.76); no increased risk was observed in the

fourth quartile. The HR for high-risk PrCA was the highest among Blacks ($HR_{Q3\ vs.Q1}$=3.77; 95%CI:1.29-11.06). The e-DII was not associated with intermediate- or low-risk PrCA incidence.

Conclusions: Sleep disruption among young adults remained persistent during two years. Chronotype modified the association between disrupted sleep, obesity and elevated blood pressure. Pro-inflammatory diet increased risk of high-risk PrCA especially among Blacks.

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LIST OF ABBREVIATIONS

AA.....African American

AF .....Acceleration Factor

BIC..... Bayesian Information Criterion

BMI..... Body Mass Index

BPH.....Benign Prostatic Hyperplasia

CMHS .....California Men's Health Study

DBP.....Diastolic Blood Pressure

DII..... Dietary Inflammatory Index

EA ..... European American

EBS .....Energy Balance Study

e-DII.....energy-density Dietary Inflammatory Index

GLMM ..... Generalized Linear Mixed Models

GLOBOCAN .....Global Burden of Cancer Study

HR..... Hazard Ratio

KP .....Kaiser Permanente

KPNCCR.....Kaiser Permanente Northern California Cancer Registry

NSAID .....Non-steroidal Anti-inflammatory Drug

OR..... Odds Ratio

%BF .....Percent Body Fat

POMS..... Profile of Mood States

PrCA ..... Prostate Cancer

PSQI..... Pittsburgh Sleep Quality Index

PSS..... Perceived Stress Score

RMLCA ..... Repeated Measures Latent Class Analysis

SAS® ..... Statistical Analysis System

SBP ..... Systolic Blood Pressure

SE..... Sleep Efficiency

SJL ..... Social Jetlag

SOL..... Sleep Onset Latency

TMD..... Total Mood Disturbance score

TST ..... Total Sleep Time

WASO..... Wake After Sleep Onset

WHR ..... Waist-to-Hip Ratio

WHtR..... Waist-to-Height Ratio

CHAPTER 1

Introduction

Background & Significance

Most physiological and behavioral processes in humans follow approximately 24-hour cycles generated by self-sustaining internal circadian clocks (1). These free-running cycles are synchronized by environmental stimuli called zeitgebers, and the most important zeitgeber is light (2). Due to the difference in circadian entrainment characteristics, differing in their preferences for timing of daily activities people may be categorized into morning, neutral and evening chronotypes (3, 4). People with early chronotypes, the so-called "larks", wake up and go to bed at night early while those with late chronotypes ("owls"), prefer to wake up and go to bed late (3). For instance, on free days, people with morning chronotypes go to bed on average between 10 p.m. and midnight while those with evening chronotypes retire between 1 and 3 a.m. (3). Morning and evening chronotypes differ in daily rhythms of many physiological processes such as body temperature, melatonin and cortisol secretion, behavioral patterns and mood (5-7). Due to variation in circadian clock genes and environmental factors, chronotypes in populations are characterized by an approximately normal distribution from extremely early to extremely late with the majority in the middle (3, 6). In addition, chronotypes are influenced by age, sex, photoperiod of birth, genetic factors, employment status and work

schedule, race, altitude and latitude of residence, exposure to light, season, and social factors (7-11).

Hectic modern life in industrialized countries imposes on individuals multiple work and social life related demands, and, through which, a schedule that often comes into conflict with the individual's chronotype. This discrepancy (misalignment) between biological preference and social clock is called "social jetlag" (SJL) (6). Individuals with evening chronotypes tend to accumulate sleep debt during the week for which they try to compensate during the weekend. Morning chronotypes, on the contrary, tend to develop sleep debt during the weekend (6). Social jetlag can start in teenage years and continue throughout working years until retirement and, thus, may affect millions of people in industrialized countries (12).

The extreme form of circadian misalignment is caused by shift work when an individual has to work at night and sleep during the day. People with different chronotypes have different abilities to adjust to shift work (13, 14). For instance, people with morning chronotypes have decreased tolerance to shift work, particularly to night shifts (13, 14). They accumulate larger sleep debt, have poorer quality of daytime sleep and are more likely to withdraw from shift work as compared to people with evening chronotypes (13, 14). Chronic jetlag in humans, for instance, in flight attendants working in long-distance transmeridian flights, is associated with impaired cognitive function (15), menstrual disturbances (16, 17), mood disorders (18) and cancer (19). Chronic jetlag was associated with increased mortality in aged mice (20). Since the circadian clock regulates metabolism and homeostasis in many tissues, circadian disruption may predispose millions of people to chronic diseases such as obesity, metabolic syndrome,

type 2 diabetes, depression, mood disorders, cardiovascular disease and cancer, similar to what has been described among shift workers (21-29). Thus, it is important to investigate complex relationships between individual circadian preference, circadian misalignment and disease risk taking into consideration various other factors that may be involved (genetic, demographic, behavioral, environmental).

The relationships between chronotype, mood and stress have recently received a lot of attention although the underlying mechanisms are not clear (7). There is evidence of higher incidence of evening chronotype ("eveningness") among patients with psychiatric conditions such as major depression and bipolar disorder (30-33), and that eveningness is associated with depressive symptoms and elevated stress in healthy individuals (34-44). Some studies, however, argue that morning chronotype ("morningness") also may be associated with altered health (22, 45-47). In some studies, people with morning chronotypes reported difficulties staying asleep in early morning hours and had elevated morbidity assessed with Nottingham Health Profile (45). Morningness has been associated with elevated blood pressure, altered metabolic parameters (46, 48) and decreased adaptability to shift work (13, 14). It is plausible that both morningness and eveningness can be associated with mood changes; these relationships are complex and the role of other influential factors needs to be explored. Although chronotype is strongly correlated with SJL (6, 12, 37, 49), only a few studies explored the relationships between SJL, alterations in mood, and depression (6, 36, 37). Results of two studies suggested that the relationships between SJL and depression may be modified by chronotype (37, 50); however, these studies disagreed with regard to whether it is a morning or evening chronotype that predispose to depression. Thus,

studies are needed to explore the relationships between chronotype, SJL and mood or stress using a longitudinal study design (to explore the temporality) that includes mediation analysis.

There is evidence that chronotype is associated with obesity (12, 33, 51-55), and in most studies those with an evening chronotype had a higher risk (12, 33, 51, 53-56). However, some other studies either refute any association between chronotype and obesity (57) or show that morning chronotypes also have an elevated risk of obesity and even cancer (12, 22, 47). Social jetlag has been associated with increased body mass index (BMI), body fat, waist circumference, metabolic syndrome, and markers of systemic inflammation independently from sleep duration (12, 49, 58). Chronotype in combination with inappropriate social schedule causes social jetlag (6, 12); thus, it is reasonable to hypothesize that social jetlag may mediate the relationship between chronotype and obesity. The only study that explored this potential mediating role of social jetlag using mediation analysis produced conflicting results (56). Thus, interrelationship between chronotype, SJL, BMI and other adverse metabolic or psychological outcomes remains unresolved.

Recently, relationships between sleep characteristics and various health outcomes such as obesity, type 2 diabetes, hypertension, cardiovascular disease and cancer have been examined in prospective studies (59-65). Yet, in most of these studies chronotype and other sleep measures were defined based only on self-report at baseline under the assumption that they were accurately reported and did not change during the study period. To date, only a few studies have investigated the variability of sleep characteristics over prolong periods of time using objective measures such as

polysomnography or actigraphy (66-68). Thus, longitudinal studies of sleep characteristics utilizing objective measurements are needed to investigate sleep variability, especially in young adults.

Recent research suggests that if insufficient or disrupted sleep along with proinflammatory diet and low physical activity persist for many years they may be associated with increased risk of cancer, possibly via oxidative stress, inflammation, and altered immune response (28, 69, 70). The complex relationships of previously mentioned life style factors in pathogenesis of prostate cancer, especially in longitudinal studies, have not yet been studied and, thus, require further investigation. According to Global Burden of Cancer Study (GLOBOCAN) data, prostate cancer is the second most frequently diagnosed cancer in men worldwide, and its incidence rates are the highest in Australia/New Zealand, Eastern and Western Europe, and North America (71). In the United States, incidence and mortality from prostate cancer differs by race/ethnicity and socioeconomic status (72, 73). In addition, in immigrants, prostate cancer incidence increases to the levels characteristic of the destination population (74, 75). This suggests that in addition to differences in screening practices, differences in lifestyle factors may play a role.

Diet is an important lifestyle risk factor for prostate cancer and yet summary measures of the diet used in previous investigations of these relationships had some limitations. For instance, an estimation of single nutrient intakes did not account for the complex relationships between multiple nutrients in the individual's complete diet (76). Dietary patterns are difficult to standardize, and some dietary indices only assessed adherence to dietary recommendations that changed over time (77-79). Developed by the

researchers at the University of South Carolina, the Dietary Inflammatory Index (DII) allows calculations of an inflammatory potential of the individual's diet and, thus, is a biologically-based summary measure for studies of the relationships between diet and health outcomes that are strongly based on inflammatory mechanisms (80, 81). The DII was based on an extensive published literature, standardized against actual food intakes in 11 populations around the world (USA, Mexico, England, Denmark, India, Australia, New Zealand, Bahrain, Scotland, South Korea and Japan) (82), and validated in epidemiological studies against inflammation biomarkers (83). Due to its unique ability to assess the inflammatory potential of the diet, the DII would be a useful measure to investigate the pathogenesis of prostate cancer, both alone and in combination with other key lifestyle factors, namely sleep and physical activity. The latter two factors also may increase predisposition to prostate cancer via oxidative stress and inflammation (28, 84, 85).

Objectives & Specific Aims

The proposed study has the following objectives: 1) evaluate the stability of chronotype, SJL, and sleep disruption during two years; 2) examine the relationships between chronotype, SJL or disrupted sleep and obesity, blood pressure, mood states, stress and poor sleep; and 3) explore the role of inflammatory potential of diet and lifestyle factors, such as sleep and physical activity in pathogenesis of prostate cancer.

The project has the following specific aims:

Specific Aim 1: Determine whether chronotype, social jetlag and disrupted sleep change within two years. Disrupted sleep is defined by the following measures: total sleep time

(TST), sleep onset latency (SOL), wake after sleep onset (WASO), and sleep efficiency (SE).

Hypothesis: Chronotype, social jetlag and disrupted sleep remain stable within two years.

Specific Aim 2: Examine relationships between chronotype, SJL, objective sleep characteristics (TST, SOL, WASO, SE) and various health indicators including: BMI, percent body fat (%BF), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mood, stress, and poor sleep.

Hypothesis 1: People with extreme chronotype (morning or evening) are more likely to have: elevated BMI, %BF, WHR, WHtR, SBP, DBP, altered mood states (depressive symptoms), stress or disrupted sleep than those with intermediate chronotype.

Hypothesis 2: People with higher SJL are more likely to have: elevated BMI, %BF, WHR, WHtR, SBP, DBP or altered mood states (depressive symptoms), stress, disrupted sleep than those with lower SJL.

*Hypothesis 3:*People with disrupted sleep are more likely to have elevated BMI, %BF, WHR, WHtR, SBP, DBP, altered mood states (depressive symptoms) or stress than those whose sleep is not disrupted.

Specific Aim 3

Specific Aim 3, sub-aim 1: Determine whether the e-DII is associated with prostate cancer incidence and investigate potential effect modification by race.

Hypothesis 1: Men with higher (pro-inflammatory) e-DII scores will have an elevated risk of prostate cancer.

Hypothesis 2: Prostate cancer incidence among men with higher e-DII is further elevated among African-Americans as compared to other races.

Specific Aim 3, sub-aim 2: Study relationships between the e-DII and high-risk prostate cancer and the role of effect modification by race.

Hypothesis 1: A pro-inflammatory diet (as measured by the DII) predisposes individuals to an elevated risk of advanced or aggressive prostate cancer.

Hypothesis 2: The incidence of advanced or high-aggressive prostate cancer in men with higher DII is further elevated in African-Americans, with low total physical activity, short sleep duration, elevated BMI or decreased in those who use NSAID.

Study outline

Chapter 2 first introduces concepts of individual circadian preference (chronotype) and SJL followed by a review of studies of the relationships between chronotype or SJL and disrupted sleep, mood disorders, stress, obesity and basic vital signs (blood pressure, heart rate). Further, a summary of current literature on temporal patterns of sleep characteristics and insomnia is presented. Chapter 2 concludes with the review of the current knowledge about the relationships between individual's diet, physical activity and sleep and prostate cancer risk. Chapter 3 describes research methods used for each specific aim, including description of data sources and analytical methods.

Chapter 4 is a manuscript for Specific Aim 1: Temporal pattern of chronotype, social jetlag and disrupted sleep within two-year time frame. Chapter 5 is a manuscript

addressing Specific Aim 2: Relationships between chronotype, SJL or sleep characteristics and anthropometric indices of obesity, blood pressure, mood and stress.

Chapter 6 is a manuscript on Specific Aim 3: Relationships between diet, physical activity and sleep and prostate cancer risk. Chapter 7 includes overall summary and suggestions for the future research.

CHAPTER 2

Literature review

Introduction to chronotypes

Most physiological and behavioral processes in humans have a diurnal rhythm (1). This daily rhythm is generated by a self-sustaining internal circadian clock located in the suprachiasmatic nuclei of the brain (2). The central circadian clock generates rhythms that are slightly longer than 24 hours; thus they have to be synchronized (or entrained) by environmental stimuli to be more closely aligned with the 24-hour light dark cycle (2). The most important synchronization stimulus (zeitgeber) is light (2, 86). Due to differences in genetic predisposition and circadian entrainment stimuli, individuals differ in their preferences for timing of daily activities and are typically categorized into morning, neutral and evening chronotypes (3, 4). People with early chronotypes, the so-called "larks", wake up early and go to bed early, between 10 and 11 p.m., while those with late chronotypes ("owls"), prefer to wake up later and go to bed later, between 11 p.m. and 1 a.m. (3). Chronotype is an individual trait influenced by genetic predisposition (9, 87), possibly photoperiod of birth (7), and modulated by environmental (geographic location of residence and light exposure) (7), and social factors (36). Due to variation in circadian clock genes and environmental factors, chronotypes in populations have an approximately normal distribution from extremely early to extremely late with the majority in the middle (3, 6). Chronotype may vary by age and sex. For instance, children

tend to have early chronotypes that gradually progress to late chronotypes reaching the peak of "lateness" in early adulthood (20 years) and then gradually become earlier and earlier for the rest of their life (88). Women reach the peak of their chronotype eveningness slightly earlier than men, and then, on average, have earlier chronotypes than men until the age of 60 years when chronotypes become very similar for both sexes and earlier than they were in childhood (88).

Social jetlag

Due to the differences between biologically preferred and social schedules (e.g. school, work), individuals with evening chronotypes accumulate sleep debt during the week for which they compensate during the weekend. Morning chronotypes, on the contrary, develop sleep debt during the weekend (6). They delay their bed time due to social interactions with later chronotypes but cannot sleep longer the next morning because of their circadian rhythm determined earlier wake-up time. This discrepancy between biological preference and social clock is called "social jetlag" (6). Originally, the term "jetlag" was described in relation to transmeridian travel as a complex of characteristic symptoms: difficulties falling asleep or staying asleep at night followed by daytime fatigue, loss of concentration, irritability, altered appetite and bowel irregularity due to the phase shift that occurs between the body's internal clock and the ambient light-dark cycle in the new location (89, 90). The major difference between aforementioned two types of jetlag is that while travel-associated jetlag is transient, social jetlag is chronic and may adversely affect mood and behavior, and contribute to development of chronic health conditions such as obesity (6, 12, 49). Some suggest that in industrialized countries, over two-thirds of healthy adults are at risk of chronic social jetlag, although

few studies have addressed its potential health impacts (12, 49). An evening chronotype positively correlates with amount of sleep debt accumulated during the week (6) and thus with social jetlag (37).

Chronotype, social jetlag, and obesity

Circadian clock regulates metabolism and obesity; thus, circadian misalignment may lead to obesity and metabolic syndrome via altered metabolic processes, lack of physical activity and poor eating habits (49, 52, 91-94). Circadian misalignment may lead to lipid disregulation, decreased insulin sensitivity, impaired glucose tolerance and altered cortisol secretion (49, 52, 91). Short sleep duration has been associated with disregulation of metabolic hormones leptin and ghrelin, which increase appetite and cravings for energy dense foods (95).

In a cross-sectional study among patients with bipolar disorder, chronotype explained 19% of the variation in total body fat (after adjustment for age, sex, mood and sleep disruption), and "eveningness" was associated with increased total body fat (51). In another study, chronotype was a significant predictor of BMI in people with normal weight (BMI 18.5-<25 kg/m^2), and morningness was associated with increases in BMI (12). Social jetlag did not predict BMI in people with normal weight; however, in overweight and obese, SJL rather than chronotype was positively associated with BMI (12). Recent experimental studies show that chronotype and circadian misalignment affect glucose tolerance via different mechanisms and independently from behavior (52).

Several studies found that evening circadian preference is associated with increased body weight in different age groups (33, 53-55). Depressed peri- and post-

menopausal women with evening chronotype and delayed mid-sleep time had higher BMI and were prone to weight gain compared to those with morning chronotypes and less delayed mid-sleep phase (33). Delayed mid-sleep time was associated with increased risk of obesity in elderly men and women in two cohort studies of Osteoporotic Fractures (96). In a follow-up study of healthy college freshmen, evening chronotype was associated with increase of BMI while there was no change among morning and neutral chronotypes combined in one group (53). A recent cross-sectional study supports this observation that evening chronotypes are more likely to have higher BMI than intermediate and morning chronotypes combined in a representative sample of US adults 18-71 years old (55). In another cross-sectional study in adolescent girls, however, evening chronotype was not associated with increased BMI (57). The mechanism underlying the relationship between chronotype and obesity has not yet been established. It is possible that some other factors such as short sleep duration, sleep/wake disturbances, stress-behavioral patterns (changes in diet or physical activity), or mood may play a mediating role. Some studies suggest that persons with late chronotype, especially those who are depressed, have increased appetite and carbohydrate cravings (33) and consume unhealthy foods (93, 94) that predispose them to obesity. In a cross-sectional study of US adults aged 18-71 years, relationships between chronotype and BMI were mediated by self-control (55). Chronotype and social jetlag are moderately correlated, especially on work days, and people with evening chronotypes tend to have more social jetlag (6, 12, 37, 49, 58). Social jetlag has been associated with increased BMI, body fat, waist circumference, metabolic syndrome, and markers of systemic inflammation (12, 49, 58). Chronotype in combination with social schedule can elicit

increase in social jetlag (6, 12); thus, it is reasonable to hypothesize that social jetlag may mediate the relationships between chronotype and obesity. The only study that explored this potential mediating role of social jetlag using mediation analysis produced conflicting results (56). One hundred thirty seven college freshmen attending an urban US university were enrolled in the study during the second week of the fall semester, and fifty-four of them were followed up eight weeks later (53, 56). Upon enrollment and at the follow-up, the students completed several self-administered questionnaires including the 5-item reduced version of Morningness-Eveningness Questionnaire used to define chronotype (97). Their chronotype did not change significantly during the study period, and a sensitivity analysis showed that completion status and chronotypes were not related (53). Those who completed the study did not differ from noncompleters by weight, BMI, sleep quality and physical activity at the baseline. The authors used linear regressions to model changes of BMI and mood during the study period based on chronotype (53). In the mediation analyses, the direct effect of chronotype on BMI could not be evaluated because of the violation of the two key assumptions, normality (for BMI) and statistical significance of the association between exposure (chronotype) and outcome (BMI); therefore, only the indirect effect was studied using a nonparametric bootstrap approach (56). Chronotype was modeled as a dichotomous variable; evening chronotypes were compared to morning and neutral chronotypes combined in one group due to the very small number of participants with morning chronotypes (56). The bootstrap analysis showed that evening chronotypes had higher SJL and the latter was associated with increase in BMI. This suggests that chronotype has indirect effect on BMI through the SJL; however, the final test for mediation (Sobel test) was not statistically significant

(56). Post hoc analyses showed that when chronotype was modeled as a continuous variable, later chronotype increased BMI via increase in SJL, and this conclusion was supported by a statistically significant Sobel test (56).

Some researchers evaluated relationships between chronotype, social jetlag and measures of obesity by incorporating both chronotype and social jetlag into their statistical models at the same time (12, 58). This approach may introduce multicollinearity which can increase the potential for Type 2 error (false negative). We propose to start with an evaluation of the correlation between chronotype and social jetlag and then conduct mediation analyses between chronotype and SJL as they relate to the metabolic and psychometric outcomes included in this study. The results of the mediation analysis will help develop an unbiased understanding of the roles of these factors in physical and psychological health.

Few studies have investigated relationships between chronotype/social jetlag and overweight/obesity. Circadian disruption is highly prevalent in industrialized countries and may contribute to obesity or other adverse metabolic outcomes. The Energy Balance data will allow for an examination of these questions in a longitudinal study with 2-years of follow-up; the planned analyses will use BMI, BF%, WHR, and WHtR. While BMI is more convenient and widely used, it is only a surrogate measure and has been shown to underestimate obesity (98-100) since it doesn't distinguish between fat and muscle tissue (101). BF% measured by dual X-ray absorptiometry is considerably more precise than BMI; it measures bone, muscle and fat tissues simultaneously (98). In addition, waist circumference and waist-to-hip ratio seem to require ethnic-specific cut-off points that makes their use for screening complicated (102). Another anthropometric index, waist-to-

height ratio (WHtR) is a better predictor of central obesity-related outcomes as compared to BMI and waist circumference (103). Thus, it has been suggested for use as a global screening index with cut-off point 0.5.

Chronotype, social jetlag, and basic vital signs

Blood pressure (BP) has wide circadian variation determined by internal and external factors. In healthy normotensive individuals blood pressure rises abruptly upon waking up and is the highest in the morning, slightly decreases after meals and is the lowest during night sleep (104). Blood pressure varies by sex; men usually have higher BP and lower resting heart rate (HR) than women (104, 105). During the day, there are 2 BP peaks, at 9 a.m. and 7 p.m., and a slight nadir at 3 p.m. The internal or circadian regulation of BP and HR occurs via hormones, peptides and neurotransmitters which all have their own circadian rhythms (104). External factors affecting blood pressure include physical activity, diet and sleep (106). Evening chronotypes tend to have higher systolic blood pressure and heart rate and lower heart rate variability than people with morning chronotypes, whereas no significant difference was observed for diastolic blood pressure (44, 105). In two studies, evening chronotypes had higher SBP and HR after being exposed to stress (44, 105). Social jetlag may affect the cardiovascular system. For instance, in a recent pilot study among rotating shift workers, social jetlag positively correlated with resting HR (107). Larger longitudinal studies are needed to confirm those relationships. Since chronotype and SJL have been associated with cardiovascular pathology and type 2 diabetes (46, 49, 107), more research is needed to explore relationships between chronotype/social jetlag with basic physiologic characteristics such as BP and HR. This information may be useful in the future to develop lifestyle

recommendations to prevent cardiovascular complications and type 2 diabetes in people with different chronotypes.

Chronotype, mood and perceived stress

Little is known about relationships between chronotype and mental health. Individuals with evening chronotype tend to have psychiatric conditions, such as major depressive disorder, bipolar disorder, anxiety or addiction disorder, or insomnia, and their depression symptoms are more severe (30-33, 108). It is difficult to make a conclusion whether mental condition affects chronotype or vise versa due to the cross-sectional nature of these studies (30, 31, 33, 57, 109). Studies in healthy individuals also revealed that people with evening chronotypes were more likely to have depressive symptoms (34-42, 110), experience higher level of stress (34, 43, 44, 111) and complain about poor health (10, 34, 110). Healthy individuals with evening chronotypes were more likely to have seasonal variation of mood and behavior and experience burnout, consume stimulants, coffee, caffeinated soft drinks and alcohol, to smoke and to consume 'fast food' than those with morning and neutral chronotypes (41, 53, 93, 110, 112, 113), although not all studies support this observation (34). Some studies report that morningness also may be associated with altered health (22, 45-47). For instance, people with morning chronotypes have difficulty staying asleep in early morning hours and report elevated morbidity elicited by Nottingham Health Profile questionnaire (45). In one study, young people with morning chronotype had a higher lifetime risk of any of the DSA IV Axis one disorders (e.g. major depressive episode, schizophrenic episode, panic attack), although, people with evening preference had higher odds of having three and more of those disorders (110). Morningness has been associated with a higher cortisol

awakening response (48), and elevated systolic blood pressure, blood glucose, low density lipoprotein and total cholesterol levels compared with evening types (46). Total sleep deprivation for 24 hours in healthy people with a morning chronotype led to increases in depression-dejection symptoms, whereas depression-dejection symptoms decreased among evening chronotypes (50). This may help explain why people with morning chronotypes have decreased tolerance to shift work, particularly to night shifts (13, 14). They accumulate larger sleep debt, have lower quality of daytime sleep and more likely to withdraw from shift work as compared with evening chronotypes (13, 14). There is an evidence that the relationship between morningness-eveningness preference and stress can be mediated by perceived sleep disruption (111), and the relationships between chronotype and depression can be modified by BMI (57). Thus, the role of various other factors in the relationships between chronotype, perceived stress and altered mood also should be taken into consideration.

Social jetlag and mood disorders

Studies of SJL and mood disorders indicate that SJL is associated with depression and smoking (6, 37). Rural Brazilian residents with more than two hours of SJL had higher depression scores compared to those with two hours or less (37). However, in another study SJL was not associated with depression (36). It is possible, that SJL, rather than chronotype, predisposes to depressive mood as it has been shown for smoking (6). Social jetlag strongly correlates with chronotype (6, 12, 37, 49), and there is some evidence suggesting that the relationships between SJL or sleep deprivation and depressive mood may be driven by chronotype (37, 50). For instance, rural Brazilian residents with up to two hours of SJL ranked by their mean depression scores from the

highest to lowest in the following order: intermediate, morning and evening chronotypes (37). The mean depression scores for two other groups of larger SJL (>2-4 and >4 hours) were not presented due to the small sample size, and SJL-depression relationship was statistically significant only among people with ≤ 2 hours of SJL (37). In agreement, in an experimental study among healthy people following 24 hours of sleep deprivation, depression-dejection symptoms increased among people with morning chronotypes and significantly decreased in those with evening chronotypes (50). After partial sleep deprivation (participants went to bed at their regular time and were awoken at 1:30 AM), depression-dejection scores in morning chronotypes did not significantly change while in evening chronotypes they decreased (50).

Temporal patterns of sleep characteristics

There is a multitude of sleep disorders and the most common of them is insomnia (114); thus, it will be used as an example of "disrupted" or "bad sleep". The proposed study, however, will not be limited to insomnia. Insomnia is can be defined as difficulty falling asleep, staying asleep, or decreased sleep quality despite having opportunities for sleep with the following day time impairment (115). Because different epidemiological studies define insomnia different ways, the prevalence of insomnia symptoms and insomnia diagnosis varies between studies and populations (116). The prevalence of insomnia symptoms in adults is 33-50% and the prevalence of general insomnia disorder (insomnia symptoms associated with associated functional impairment) is 10-15% (115). Studies show that insomnia may be associated with increased risk of many chronic diseases such as cardiovascular disease (117), hypertension (118), obesity (54, 119), diabetes (120), and cancer (28, 121, 122). Taking into account high prevalence of

insomnia in general population, investigation of its role in development of chronic diseases is very important. Recently, relationships between sleep characteristics and previously mentioned highly prevalent chronic diseases have been examined in many prospective studies (59-65). In most of these studies, information about sleep was obtained from questionnaires completed by study participants who were asked to provide average estimates for previous time periods of different length. Thus, these studies assume that self-report accurately describes the individual's sleep and sleep characteristics do not change over time. On the contrary, it has been shown that sleep disruption assessed by self-report differs from sleep assessed using objective measures (123, 124). For instance, healthy young individuals in one study overestimated their sleep onset latency and underestimated frequency of awakening (124). In another study, participants with chronic insomnia underestimated their total sleep time and number of awakenings but overestimated sleep onset latency (125). Only a few studies have investigated the variability of sleep characteristics over prolong periods of time using objective measures such as polysomnography or actigraphy (66-68). In middle-aged people, sleep measures, such as sleep duration, efficiency, latency and time in bed showed considerable day-to-day variability, however, they were stable during the 1-3 year follow-up (66-68). In college students aged 18-40 years, longitudinal studies assessed sleep based only on self-report and yielded contradictory results; both studies were conducted during the spring semester (126, 127). Among undergraduate students, for instance, sleep duration decreased and the number of awakenings increased as the semester progressed (126). In another study, however, the sleep duration and quality

increased within a 3-month long semester (127). Thus, a prospective study design is proposed to study the consistency of actigraphic sleep measures over time.

Diet, sleep, physical activity, and prostate cancer

Chronic inflammation predisposes individuals to many chronic diseases, including cancer, and may contribute to development of more aggressive form of the disease (128, 129). Among agents predisposing to chronic inflammation are infections, poor diet, disrupted or insufficient sleep, obesity, smoking and immunosenescence, or age-related diminution of immune response (130-133). Continuous exposure to antigenic stimulation and stress compromises the ability of the aging immune system to cope with such stimuli, which in turn leads to chronic inflammation, the so-called "inflamm-aging" (134).

The role of inflammation in carcinogenesis has been described for several cancers, such as colorectal, lung, liver, bladder, cervical and pancreatic (135). Additionally, a relationship with inflammation has been suggested for prostate cancer (136, 137). Inflammation is frequently detected in different prostatic conditions, such as prostatitis, benign prostatic hypertrophy, and prostatic intraepithelial atrophy (138-140). On average, 11-16% of men in the United States are diagnosed with prostatitis in their lifetime (141). About 20% of men with inflammation detected during prostate biopsies developed prostate cancer within 5 years, and additional 6% were diagnosed with high-grade prostatic epithelial neoplasia, which is considered a precursor of prostatic adenocarcinoma (136).

There is evidence that inflammation within the prostate is strongly associated with oxidative stress, which has been shown by multiple experimental, epidemiological and clinical studies to play an important role in the pathogenesis of prostate cancer (142). Inflammatory cells present at the sites of chronic prostate inflammation produce increased amounts of reactive oxygen species (ROS) (143) that, over time, cause DNA mutations, promote genetic instability and cellular senescence and, therefore, can contribute to the initiation of carcinogenesis (144). In addition, prostate cancer cells themselves produce high quantities of ROS, which can play important role in tumor growth and development of a malignant phenotype (145). Increased levels of ROS combined with inability of antioxidant systems to neutralize them lead to chronic state of oxidative stress (146). Oxidative stress that occurs via tissue damage and the corresponding recruitment of more inflammatory cells lead to the perpetuation of chronic inflammation, which completes the vicious cycle (147).

Recent research identified a few modifiable risk factors - diet, physical activity and sleep duration and disruption that have been shown to affect inflammation, immune response and oxidative stress (28, 69, 70); however, further research is needed to elucidate the role of these factors in pathogenesis of prostate cancer. Taking into account the high incidence of prostate cancer in Western countries, developing strategies that target these potentially modifiable risk factors is a high priority for public health. In the United States, prostate cancer incidence and mortality rates vary by race and are the highest among African-Americans (72, 73). According to age-adjusted estimates for 2013, prostate cancer incidence in African Americans is 70% and mortality is 2.4 times higher than in European Americans (72, 73). African Americans tend to be diagnosed at a

younger age and with more aggressive disease than their European-American counterparts. Prostate cancer incidence and mortality in Hispanics/Latino and Asian-Americans are lower than in African- and European Americans (73). Migrant studies show that prostate cancer incidence and mortality in immigrants to the United States are higher than in their countries of origin which suggests the involvement of environmental, behavioral and lifestyle factors (74, 75).

It has been proposed that racial/ethnic disparities in health status may be due to differences in access to healthcare, socioeconomic status, cultural factors (e.g. diet, utilization of health care, religious beliefs) and genetic predisposition (73, 148); thus, it is important to explore complex relationships between multiple modifiable risk factors and prostate cancer risk/aggressiveness by race/ethnicity. It has been shown, that racial/ethnic minorities are more likely to have a sedentary life style and a bad diet with low consumption of fruit and vegetables as compared to non-Hispanic Whites, and this lifestyle pattern is associated with high levels of systemic inflammation, as expressed by increased levels of C-reactive protein (CRP) (149-151).

Among the dietary factors that have been proposed to decrease prostate cancer risk are tomatoes and lycopene, cruciferous vegetables, green tea, soy, vitamin E, and selenium (152-154). The protective effects of selenium and vitamin E intakes, however, were not confirmed in a recent double-blind placebo-controlled Selenium and Vitamin E Cancer Prevention Trial (SELECT study) (155). The potential mechanism of anticancer effect of plants mentioned above and vitamin E works through protection of cells and DNA from oxidative stress (156). Phytochemicals contained in cruciferous vegetables, kale, cauliflower and Brussels sprouts, in addition to antioxidative, also have pro-

apoptotic (157), anti-proliferative and anti-metastatic effects in prostate cancer cells *in vitro,* and in animal models (158). Excessive intake of total dietary energy, meat, dairy products, calcium, total and animal fat, and beta-carotene, on the contrary, may predispose to increased prostate cancer risk (152-154). According to some theories, excessive intake of fat and red meat can promote carcinogenesis within the prostate via increased insulin growth factor (IGF) and damage by ROS (156). Caloric restriction reduces oxidative stress and related damage *in vitro* and in animal models (159).

Although analyses of single nutrients and foods are a common practice, they are inherently flawed because they do not account for possible interactions between nutrients and fail to evaluate joint effects of diet on health outcome (76). More recent approaches use diet quality scores and dietary patterns to evaluate a combined effect of food usually consumed on disease (77). For instance, higher Healthy Eating Index and Alternate Healthy Eating Index-2010 values were associated with decreased risk of total prostate cancer, while no association was detected for the alternate Mediterranean Diet score (78). A few studies examined relationships between dietary patterns and prostate cancer and yielded inconsistent results (76, 79). The use of diet quality scores and dietary patterns has inherent shortcomings. For instance, the diet quality scores only measure adherence to the recommended diet and fail to account for ethnic variability within and between populations (77). Dietary pattern analysis lacks standardization, which impairs generalization, complicates comparisons between studies and is more suitable for hypothesis generation rather than testing (77).

Developed by researchers at the University of South Carolina's Cancer Prevention and Control Program, the dietary inflammatory index (DII) is a unique approach which

allows for calculation of the overall inflammatory score of the individual's diet from maximally anti- to maximally pro-inflammatory. More negative scores are associated with anti-inflammatory potential, whereas more positive scores are indicative of more pro-inflammatory potential (80, 160). The major advantage of DII over other dietary indices is that it measures the inflammatory potential of the individual's diet based on actual intakes. The individual's DII scores are standardized against range of actual food intakes observed in 11 different populations around the world, which facilitates comparability between existing and future studies (160). Another important advantage of the DII is that it gives comparable results if calculated using different methods of dietary assessment, which facilitates its use by epidemiological studies of different design and different dietary assessment methods (161). DII scores have been shown to predict levels of inflammatory markers and risk of chronic disease in several studies (80, 82, 161-180). Several of these studies investigated the relationships between DII and breast, esophageal, pancreatic, and colorectal cancers (164-166, 174, 180). One case-control study has investigated the relationships between DII and prostate cancer risk among Jamaican men (181). Men in the highest quartile of DII score had 2.4 times increased risk of prostate cancer as compared to those in the lowest quartile (aOR=2.39; 95% CI:1.14-5.04). This suggests that a diet with the higher proinflammatory potential may increase individual's risk of prostate cancer; however, this finding needs to be confirmed in longitudinal studies with larger sample sizes that include participants of different race/ethnicity.

CHAPTER 3

Methods

Specific Aims 1 & 2

1. Study population

For Aims 1-2 was used previously collected data from the Energy Balance Study (EBS) conducted by researchers from the University of South Carolina, Columbia, SC (182). The EBS is an ongoing three-year longitudinal study investigating effects of energy intake and expenditure on changes in body weight, body composition and health indices in healthy young adults. In 2011, the EBS recruited 430 healthy men and women who were 21-35 years of age and had a BMI of 20-35 kg/m^2. This population group was studied since they may be at risk for weight gain and an increase in body fat as they approach middle age (183). The prospective participants were eligible for the study if they were 21-35 years of age, did not have any major health conditions, did not change their health behavior within preceding 6 months, and did not plan to relocate within the next 15 months (182). The participants were excluded if they had history of major depression, anxiety or panic disorder, took serotonin reuptake inhibitors, used medications to lose weight or stop smoking within previous 6 months. Women were excluded if they gave birth within previous 12 months, changed their birth control regimen within the 3 previous months, were pregnant, or if they planned to start or stop birth control medication within the following 3 months (182). All otherwise eligible

prospective participants were excluded if they had systolic blood pressure ≥150 mmHg and/or diastolic blood pressure ≥90 mmHg or a blood glucose level >145 mg/dl as diagnostic criteria for hypertension and diabetes, respectively. The EBS was approved by the Institutional Review Board at the University of South Carolina, and all study participants signed informed consent.

2. Energy Balance Study data collection procedures

The participants were initially screened for demographic and health-related inclusion/exclusion criteria via email and then additionally screened over the phone. All eligible study participants attended an orientation session where they were provided the information about the study and had their height and weight measured to verify their BMI. Within three weeks following the orientation, the participants had three baseline measurement sessions. During the first baseline session the participants provided detailed demographic information and a medical history and completed psychometric and activity questionnaires. Resting blood pressure, weight, height, hip and waist circumferences, and body composition were measured during the second baseline session. For the third baseline session, the participants had to fast for 12 hours and to abstain from physical activity for 24 hours. During this session weight, height, hip and waist circumferences were measured again, and the participants received a SenseWear® Mini Armband (SWA) (BodyMedia Inc., Pittsburgh, PA) to monitor their physical activity and sleep over 10 days (182). During these 10 days, licensed dietitians conducted three 24-hour dietary recalls by phone; two on randomly selected week days and one on a weekend. These dietary recalls elicited information about all the food participants consumed during the previous 24 hours. The follow-up assessments were conducted quarterly up to 24 months.

Upon completion of all follow-up sessions the study participants were given incentives: $500 and a report containing the information on their energy intake and expenditure, body weight and composition, resting metabolic rate, and cardio-respiratory fitness levels.

3. Sleep measures

The sleep measures were derived from the Armband data. The SenseWear® Mini Armband is a portable device 8.8×5.6×2.1 cm in size, 82 g weight, worn over the triceps muscle of the right arm and has micro-electro-mechanical sensor detecting and measuring limb movements (184). The sensor is monitored 32 times per second and data were recorded at 1 minute intervals. The SWA data by minute are analyzed using SenseWear Professional® Research Software (Version 7.0, Body Media® Inc.). The demographic information (i.e. age, sex, height, weight and smoking status) was used to customize proprietary algorithms. The SWA data yields several average night-time sleep measures: sleep onset and wake-up times, TST, SOL, WASO, and SE (185). The sleep onset time was determined by the first out of three minutes asleep that coincided with ≥10 minutes lying down (185). Morning wake-up time was defined by the first out of 90 consecutive minutes awake (185). Sleep duration is the sum of all minutes asleep during one sleep bout (185). The ability of the SWA to measure sleep was validated against polysomnography and found to be adequate (184). For each study participant all measures were averaged across the entire period of wearing of the SWA (4-10 days). Day-to-day variability in sleep characteristics exceeded the long term variability (68). Previous studies showed that five to seven nights of actigraphy are sufficient to obtain reliable estimates of sleep duration (68, 123, 186). The study participants were instructed

to take the Armband off only when it could get wet (showering or bathing) and to keep a log of their activities during all times when the Armband was not worn (182). Activities from the log were matched to activities in the 2011 Compendium of Physical Activity (187), and corresponding metabolic equivalent was multiplied by individual's resting metabolic rate which allowed to calculate energy expenditure and sleep characteristics during non-wear periods (182). Total physical activity minutes were calculated for activities equal to or exceeding 1.5 metabolic equivalents (185). Physical activity was used as a continuous measure. Only observations with actigraphy data on 4 or more nights were considered complete and used in this study.

3.1. Chronotype

Chronotype was defined as the time of mid-sleep on work days corrected for "make-up sleep" on free days (12). For detailed chronotype calculations see Appendix A.

3.2. Social jetlag

SJL was defined as a difference between midpoints of sleep on a weekend (unadjusted) and on week days (12). An absolute value of the social jetlag was used for all analyses where SJL was an independent variable.

3.3. Total Sleep Time

TST was categorized as <6, 6-7, and ≥7 h (185). Two sleep duration measures were used for all analyses: average for all days of actigraphy (week days and weekend days) and average on week days only. The upper cut-off point 7 h was selected due to the insufficient sample size that we would have if we selected cut-off point ≥8 h, which is frequently used in other studies (96, 119, 188). Moreover, several studies showed that

individuals tend to overestimate their average sleep duration by 1 hour and more as compared with objective measures (e.g. actigraphy) (189, 190).

3.4. Sleep onset latency

SOL is a time that a person spends in bed before he/she falls asleep. In EB study, sleep onset latency was calculated using SWA data as time between lying down and sleep onset (185). According with clinical guidelines, sleep onset latency of >30 min is considered one of the symptoms of insomnia (115). However, in the EBS population, less than 5% of participants had sleep onset latency >30 min at any one of five time points. Thus, the more relaxed cut-off point of 12 min (≥12 vs. <12 min) was used (191).

3.5. Wake After Sleep Onset

WASO was calculated from SWA data as a sum of wake periods of ≥2 min each after sleep onset and until the final wake-up time (185). To be consistent with the previous studies that used wrist actigraphy, WASO was dichotomized (<60 min, ≥60 min) (119, 188).

3.6. Sleep efficiency

SE was calculated as a proportion of TST from the length of the night sleep bout (185). Naps were excluded. SE was used as a continuous and a categorical variable; the latter was dichotomized according with clinical guidelines for insomnia (≥85% vs. <85%) (115).

3.7. Naps

Naps were defined as sleep bouts <4 hours that ended between noon and 10 p.m. or bouts <45 minutes (185). Variable nap was dichotomous (Yes/No); those with >0 min of nap were consider having a nap.

3.8. Sleep quality

Sleep quality was defined using Pittsburgh Sleep Quality Index (PSQI) obtained using PSQI questionnaire (see section "Questionnaires"). The PSQI score was dichotomized using conventional definitions of poor sleep (PSQI >5) and a good sleep (PSQI ≤5) (192). TST, SOL, WASO or SE were used as indicators of sleep disruption.

Sleep measures in this study had potential limitations. The assumption that the study participants had free days only on weekends may introduce non-differential misclassification of the exposures: chronotype and social jetlag. To address this issue, distributions of chronotype and social jetlag in the study population were compared with the distributions among participants of the same age in other studies.

4. Questionnaires

4.1. Profile of Mood States (POMS)

POMS is a self-administered questionnaire that consists from 65 adjectives and short phrases with Likert-type scale with five answer choices for each question (193). Different groups of adjectives define six factors: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, Confusion-Bewilderment, and each of those factors has its own scale. The Total Mood Disturbance Score (TMD score) is calculated by summing 5 factors and then subtracting for the Vigor-Activity score. The

Total Mood Disturbance Score and its 6 components were used separately as continuous variables. The Energy Balance study participants completed the POMS questionnaire at baseline, 12 and 24 months follow-up (Table 2.1), and all 3 aforementioned time points were used in the analyses.

4.2. Perceived Stress Scale

Perceived Stress Scale is a 10-item questionnaire where each item inquires how a subject feels or thinks and offers him/her 5 choices with increasing value from never to very often (194). The positive items are reverse scored. All scores are summed to yield the total score ranging from 0 to 40. A higher score indicates a higher stress level. The Perceived Stress Scale was validated in different populations, found to be a better measure of overall stress as compared to objective measures of stressful life events, and recommended for studies investigating relationships between stress and disease outcomes (194-196). The Perceived Stress Score (PSS) was used as a stress measure at 3 time points (baseline, 12 and 24 months follow-up) (Table 2.1). The Perceived Stress Scale is not a clinical test; therefore, there are no established cut-off points. To categorize PSS, some studies used a median split (194, 197) while others used quartiles (198). PSS in the EBS sample had approximately normal distribution and was modeled as continuous and categorical variables with the median as a cut-off point (<12 vs. ≥ 12).

4.3. Pittsburgh Sleep Quality Index (PSQI)

PSQI ascertains information on seven areas of sleep during the previous month (192). The respondents self-score each of the seven components using a Likert scale from 0 to 3, where 3 is assigned to the highest negative extreme. The sum of scores for all

individual components yields the total PSQI score (192). It was administered at baseline, 12 and 24 months follow-up (Table 2.1). The PSQI was used as an indicator of sleep quality: poor sleep (PSQI >5), and a good sleep (PSQI ≤5) (192).

5. Anthropometric measures

For the assessment of all anthropometric measurements the participants were dressed in scrubs and had bare feet. Their height and weight were measured using traditional stadiometer and electronic scales with a precision of 0.1 cm and 0.1 kg, respectively. The average of three measurements was used to calculate BMI (weight (kg)/height (m^2)). To measure waist and hip circumferences, a calibrated spring-loaded tape measure was used. The waist circumference was measured at mid-point between costal margin and iliac crest on the axillary line on both sides of the trunk and 2 cm above the umbilicus (182). The hip circumference was measured at the level of the greater trochanter, at the widest point. The average of three measurements rounded to 0.1 cm was recorded. Body composition was measured using dual x-ray absorptiometry full body Lunar fan-beam scanner (GE Healthcare model 8743, Waukesha, WI).

BMI was categorized into two groups: underweight and normal weight (<25 kg/m^2); overweight and obese (≥25 kg/m^2) (199). BF% was dichotomized using the guidelines by the American Society of Bariatric Physicians (ASBP) and American Medical Association (AMA) specialty board (2009) that defined obesity as BF% ≥25% in men and ≥30% in women (98). A recent meta-analysis showed that cut-off points for BF% >25% in men in > 30% in women were the most sensitive for obesity (99). Waist-to-hip ratio will be dichotomized: <0.95 vs. ≥0.95 in men and <0.80 vs. ≥0.80 in women (200). Waist-to-height ratio will be dichotomized as <0.5 vs. ≥0.5 (103). An average of

two resting blood pressure measurements were categorized into two groups: SBP ≥120 vs. <120 mmHg, and DBP ≥ 80 vs.<80 mmHg.

6. Covariates

Estimates of total daily physical activity time were obtained from armband data. Information for the periods of non-wear was supplemented with values for matching activity from the 2011 Compendium of Physical Activity (184). Total daily hours of physical activity were defined as any activity of at least 5 metabolic equivalents. Time napping was obtained from armband data. Dietary information was collected using three 24-hour dietary recalls conducted by phone; two on randomly selected weekdays and one on a weekend. The Nutrient Data System for Research (version 2012: Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota) was used to estimate nutrient and individual food intakes from the dietary recalls. Forty three food parameters and nutrients were further used to calculate a dietary inflammatory index (e-DII) that expresses an inflammatory potential of individual's diet (81). Lower DII scores are anti-inflammatory while the higher scores are more proinflammatory, and the maximum theoretical range is −8.87 to 7.98. To account for individual differences in energy intake, the DII scores were calculated per 1,000 kilocalories (4,184 KJ) (e-DII) as previously described (185).

7. Exclusion criteria

All 430 participants of the EBS were eligible for the proposed study. Individuals were excluded from statistical analyses if their armband data had the following deficiencies: missing bed time or wake time, <4 days of actigraphy in any given assessment period, missing sleep data on the weekend, extreme or implausible TST

values (<4 hours either on week days, free days, or on average, TST >11 hours on work days or on average), and when mid-sleep on free days occurred in the afternoon (12). In addition, participants were excluded from all analyses if they regularly used (≥3 times per week) sleep promoting medications (over the counter or prescription), worked night shifts, or traveled across meridians during periods of armband wear. The final analytical dataset consisted of 390 participants (1,431 repeated observations).

7. Statistical analyses plan

Specific Aim 1

The first specific aim was to determine whether chronotype, social jetlag, and sleep disruption change within two years. For these analyses was used SWA data at five time points (baseline, 6, 12, 18, and 24 months). The analytical dataset consisted of 390 participants (1,431 repeated observations).

Regression approach

First, descriptive statistics, distributions for continuous data and frequencies for categorical variables were analyzed. Further, the bivariate relationships between time, chronotype, SJL, objective sleep measures (TST, SOL, WASO, SE), and potential covariates were explored using simple subject-specific Generalized Liner Mixed Models (GLMM) with GLIMMIX procedure in SAS® (version 9.4, Cary, NC). This method accounts for correlations between repeated measurements through the inclusion of an additional variance component (201). Each subject in this study was considered a cluster of observations. The following covariates were considered: sex (male, female), race (European American [EA], African American [AA], Other [Hispanic, Asian, Native American or mixed race]), education (high school graduate/GED some college, college ≥

4 y.), income (<$20,000, 20,000 to <40,000, 40,000 to <60,000, 60,000 to <80,000, ≥80,000), employment (student/other, employed and self employed), marital status (married, single), having children (yes/no), physical activity (h), caffeine intake (g/d), e-DII, napping (yes/no), and season (winter [November-January], spring [February-April], summer [May-July], autumn [August-October]), and current dieting (yes/no). Potential covariates with p-value <0.2 in bivariate analyses were selected for inclusion in full statistical models. Time was the main independent variable for all analyses. Separate multivariable statistical models were built for chronotype, SJL and objective sleep measures (TST, SOL, WASO, SE) as continuous dependent variables. Manual backwards elimination was used to identify covariates for inclusion in the final model that changed the effect estimate of the main exposure variable by ±10%. Variables that were statistically significant (p≤0.05) also were included in the final model.

Latent class analyses

RMLCA was performed using PROC TRAJ in SAS® to identify latent groups for each continuous variable (absolute SJL, chronotype, TST, SOL, SE, WASO) (202, 203). This procedure uses a mixture model approach to define the trajectories of unique subgroups within a population that don't change their group membership over time (204, 205). The best fitting crude model was selected using Bayesian Information Criterion and comparing differences between simple and more complex models (205). The final selection of the number of latent groups was based on the best model fit and minimum group sizes containing ≥10% of the study population. Analyses for chronotype, TST and SE were adjusted for race (EA vs. AA or Other) and sex, which were assumed not to change over time. WASO was adjusted for race only. Absolute SJL and SOL were not

adjusted for race or sex because latent groups were not influenced by these variables. Since the group trajectories for each measure were linear, potential covariates that change over time were not examined. Only participants with at least three assessments during the study period were included into these analyses (n=312, 1,297 observations).

Finally, bivariate GLMM were used to identify demographic and other characteristics that differed among the latent classes for absolute SJL and each of the sleep outcomes.

Specific aim 2

The second specific aim was to examine the relationships between chronotype, absolute SJL, objective sleep characteristics and various outcomes: BMI, %BF, WHR, WHtR, blood pressure, mood, perceived stress, and poor sleep (defined with PSQI). For the analyses involving anthropometric outcomes was used dataset with five time points (n=390, 1,431 repeated observations). Since data on mood, stress and poor sleep was available only for three time points (baseline, 12, and 24 months) a smaller subset of data was used (n=390, 813 observations) for these analyses.

Descriptive analyses were conducted first. They included analyses of distributions for continuous and frequencies for categorical variables. Bivariate associations between chronotype, SJL, objective sleep measures, mood, perceived stress, poor sleep, and potential covariates (see specific aim 1 above) were explored next using GLMM with repeated measures. Potential covariates with p-value <0.2 in bivariate analyses were selected for inclusion in full statistical models. Manual backwards elimination was used to identify covariates for inclusion in the final model that changed the effect estimate of

the main exposure variable by ±10%. Variables that were statistically significant ($p \leq 0.05$) also were included in the final model. When examining relationships between SJL or sleep measures and the anthropometric outcomes, mood and stress, chronotype (continuous) was considered as a potential confounder along with other covariates.

RMLCA analyses using PROC TRAJ in SAS® were used to identify three latent groups for chronotype as was described above. Any time points with complete SWA data were included into these analyses. Since the group trajectories for all three latent chronotype groups (morning, intermediate and evening) were linear, other potential covariates that change over time were not used to adjust trajectories. Adjusted means of SJL and all objective sleep characteristics by latent chronotype group were compared using F-test with PROC GLIMMIX. The intermediate chronotype was used as a reference group. This categorical chronotype variable was used as a main independent variable in the GLMM evaluating the relationships between chronotype and anthropometric measures. To explore a possibility that the relationship between SJL, other sleep characteristics and anthropometric measures were modified by chronotype, two approaches were used. First, an interaction term between a sleep measure and chronotype group were added to the final statistical model. The second approach involved stratification by chronotype group. This approach was also applied in the analyses of the relationships between absolute SJL, mood and stress.

Specific Aim 3

1. Study population

For the proposed study was used data from the California Men's Health Study (CMHS), a large multiethnic cohort of U.S. men members of Kaiser Permanente (KP), a

health insurance provider that covers a large number of residents of Northern and Southern California. The primary goal of CMHS cohort was to study the etiology of prostate cancer in populations with diverse ethnicity (206). In 2002-2003 the CMHS recruited 84,170 men of ages 45-69 years; 40% of them were from minority populations. Men were eligible for the CMHS if they had membership at KP for at least one year prior to the recruitment and were 45-69 years of age. Information about the CMHS recruitment and data collection procedures was described in detail elsewhere (206). Briefly, the study enrolled minority populations including Chinese, Latino and African Americans. The potentially eligible participants were first selected based on their last names obtained from insurance records, and a preference was given to men with Chinese and Spanish last names (206). The recruitment was conducted in three waves. First, the participants were mailed a recruitment letter and a short questionnaire inquiring about their ethnicity, anthropometrics, and a personal history of prostate specific antigen (PSA) screening, benign prostatic hyperplasia (BP), and prostate cancer. The letters and questionnaires mailed to men with Chinese last names were in Cantonese/English and in Spanish/English for all others. Also, the participants were selected from areas covered by KP plan where a high proportion of residents were African American (206). Further, men who responded to the short questionnaire and were eligible for the study were mailed a longer questionnaire. Some participants completed both short and long questionnaires on-line (206). The CHMS collected comprehensive information on participants' health status, comorbidities, family history of prostate cancer, medication and supplementation use, and potential prostate cancer risk factors such as diet, physical activity and sleep. The CMHS cohort has broad range of education and income (206). The important

advantage of enrolling study participants from among the members of the health insurance plan allows linking self-reported data with medical records and information from cancer registries. The latter provides high quality ascertainment of prostate cancer cases.

For the proposed study was used data on 43,202 participants of the CMHS followed from the time of the completion of the long CMHS questionnaire in 2002-2003. Time of the follow-up was censored at: diagnosis of incident prostate cancer, death, gap in KP membership exceeding 90 days, or the end of the study on December 31, 2014, whichever comes first. For the description of the available study population see Table 7. Participants who reported personal history of prostate and any other cancer except non-melanoma skin cancer in the baseline questionnaire were excluded (100/1,286). Participants who had caloric intake of less than 500 kcal or greater than 6,000 kcal per day were excluded from the analyses (53 with prostate cancer and 905 without prostate cancer). Indicator variables with consequent sensitivity analyses were used to preserve observations with missing data on significant confounders. For the analysis of the relationships between DII and the incidence of advanced prostate cancer, all participants with missing data on prostate cancer stage based on SEER classification were excluded (n=38, 1.36%).

2. Questionnaires used to collect the data in CMHS

2.1. Short questionnaire, as was previously mentioned, elicited information about anthropometrics, and a personal history of PSA screening, BPH, and prostate cancer.

2.2. Long questionnaire was 24 pages long, completed upon enrollment and elicited information on demographics, family history of cancer, an individual's health conditions

including those involving prostate, medication use, lifestyle factors including physical activity and smoking, diet and supplement use, marital status, education and family income during the preceding year.

2.3. Semi-quantitative food frequency questionnaire (FFQ) was the version of Women's Health Initiative FFQ modified for use in men and validated in several studies (207-209). This FFQ allowed collecting the information about habitual diet and alcohol consumption within the previous year. E-DII was calculated for all participants of this study.

2.4. Physical activity questionnaire used questions adopted from the CARDIA Physical Activity History (210). It elicited information on frequency, duration and intensity of recreational, household and occupational activities (206). Total physical activity was measured in MET-hours per week and used as a continuous variable for all analyses.

3. Prostate cancer ascertainment

The information about all prostate cancer cases diagnosed during the follow-up was obtained via linkage of CMHS members to the Kaiser Permanente Northern California Cancer Registry (206, 211). California state law requires reporting of all incident cancer cases and the KPNCCR ascertains and reports all cases according to the standards established by the National Cancer Institute's Surveillance, Epidemiology, and End Result Program (SEER). In this study, PrCA was categorized into three groups using the updated (2010) version of the standard PrCA staging system endorsed by the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) (212).

4. Measures

Exposures

The DII was calculated per 1,000 kcal (e-DII) using derived values for 27 food parameters including whole foods, micro- and macronutrients, and other food constituents (e.g. flavonoids). The information on habitual food intake used for derivation of the food parameters was elicited using previously mentioned semi-quantitative FFQ. The choice of food parameters for the DII calculation is based on previous research that entailed reading and scoring nearly 2,000 articles (160). Derived from the literature individual effects of individual DII components were standardized to global database comprised from 11 diverse populations: USA, Australia, Bahrain, Denmark, India, Japan, Mexico, New Zealand, South Korea, Taiwan, and UK (81). This approach to calculation of DII both "anchors" the individual's exposure to a robust range of dietary patterns in a variety of cultural traditions and obviates completely the problem of units because the z-scores and percentiles are independent of the units of measurement (i.e., the percentile is the same whether the parameter is expressed in ug or mg) (160). Ideally, the DII calculations are based on the total 45 food parameters, although it also can be calculated when fewer food parameters are available. For instance, the DII was previously used in the SEASONS study with the 7DDR (which yielded 28 food parameters) and in the Asclepios Study using semi-quantitative FFQ (which yielded 17 food parameters) and had observed findings consistent with those obtained from 24-hour recall interviews (which ideally yield all 45 parameters) (83, 169). From the research conducted this far, the DII is typically within the range of -5 to +5 (maximum and minimum ~-8 and +8). In the sample available for this study, the DII in all participants ranges from -6.3 to 4.7

(Table 7). The reason for the adjustment for energy is previously detected strong negative correlation of the DII with total energy intake (164). An absolute intake of each food parameter in the study population was individually modeled using a regression model with total caloric intake in the study population as an independent variable as previously described (164). The predicted energy-adjusted intake of each nutrient was calculated as a sum of the absolute nutrient intake of an individual with the mean caloric intake with the corresponding residual from the regression model. Further, energy-adjusted intakes of all individual food parameters were standardized to the world's population using z-scores and percentile scores. The individual percentile scores were then multiplied by parameter-specific inflammatory values and summed yielding the final e-DII score. For all analyses, the e-DII will be used both as a continuous variable and as a categorical variable. Since the clinically meaningful cut-points for e-DII have not yet been established, we will use the cut-off points between quartiles of e-DII distribution among men without prostate cancer.

Events of interest

For the analyses of the relationship between e-DII and PrCA risk (sub-aim 1), incident PrCA will be presented as a dichotomous variable (Yes/No). For the sub-aim 2, PrCA was categorized into three groups using the updated (2010) version of the standard PrCA staging system endorsed by the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) (212). The high-risk PrCA group included men with clinically localized high-risk PrCA and advanced, very high-risk PrCA (≥T3a or PSA>20 ng/ml, or a Gleason score of 8-10, or those who died from PrCA). The clinically localized, intermediate-risk group consisted of men with T2b-T2c,

or T1-T2a and PSA10-20, or T1-T2a and a Gleason score of 7. All other men with PrCA were in the clinically localized, low-risk PrCA group.

Statistical analysis

The follow-up time was censored at: diagnosis of incident PrCA, death, gap in KP membership exceeding 90 days, or the end of the study (December 31, 2014), whichever came first. The analyses started with descriptive statistics. The e-DII was categorized into quartiles based on its distribution among all participants. Categorical variables with strata containing <10% of the total population were recoded using indicator variables that had missing values as a separate category. Bivariate relationships between prostate cancer status and e-DII, or potential covariates, including: race (White, Black, Asian, Hispanic, Other), age at baseline (5-year intervals for the overall PrCA risk estimates and 45-55, 56-65, 65-70 years for subgroup analyses), body mass index (BMI) calculated from self-reported weight in kilograms divided by square height in meters (< 25, 25-29.9, ≥30 kg/m^2), education (high school equivalent or less; vocational or technical school; some college, associate or bachelor degree; graduate/professional school), smoking status (current or former smokers vs. non-smoker), income (<$40,000, $40,000-$59,000, $60-$80,000, $80-100,000, >$100,000), regular use of non-steroidal anti inflammatory medicines (NSAID) (Yes/No), regular multivitamin use (Yes/No), sleep duration (≤6, 7, ≥8 hrs), total physical activity (0-359, 360-1102, 1103-2201, > 2202 MET-min/week), history of diabetes (Yes/No; recorded diagnosis in the Northern California KP Diabetes Registry), family history of PrCA in a first-degree relative (Yes/No), and benign prostatic hyperplasia (BPH).Variables with a p-value of ≤0.20 will be selected for further evaluation in a multivariable model. A manual backwards selection procedure was used

to identify covariates for inclusion in multivariable models. Variables were retained in the final statistical models if their exclusion resulted in a change in the effect estimate for e-DII by ≥10%. Statistically significant covariates ($\alpha<0.05$) also were retained in the final statistical models. The proportional hazards assumption was tested using graphical (Kaplan-Meyer survival plots) and regression approaches (cumulative Martingale residuals). Effect modification was tested using two approaches: Likelihood Ratio Test (LRT) for significance of the interaction term added to the final model, and stratification of the analysis based on differing levels of the effect modifier. Cox proportional hazards models were used to assess the relationships between the e-DII and either high- or intermediate-risk PrCA. The proportional hazards assumption was violated for sleep and age; therefore, these variables were placed in the STRATA statement in the PHREG procedure in SAS®. For linear trend tests, the median of each e-DII quartile was included in statistical models as a continuous variable with adjustment for the same confounders that were included in the previous analyses.

Sensitivity analyses were conducted to explore the possible effects of missing data on the results. Men diagnosed with PrCA during the first 3 years of follow-up were excluded in order to assess the possibility of reverse causality. In separate analyses, all participants with missing sleep duration were excluded, and analyses were then repeated after removal of the sleep duration variable from the statistical models.

Table 3.1 Questionnaires and measurements used in the Energy Balance Study

Questionnaire/ measure	Time point				
	Baseline	**6 M**	**12 M**	**18 M**	**24 M**
Demographics	✓		✓		✓
Medical History	✓				
Profile of Mood States[1]	✓		✓		✓
Perceived Stress Scale	✓		✓		✓
PSQI	✓		✓		✓
Physical Activity	✓	✓	✓	✓	✓
Sleep measures	✓	✓	✓	✓	✓
Anthropometrics[2]	✓	✓	✓	✓	✓
Basic vital signs[3]	✓	✓	✓	✓	✓

PSQI: Pittsburgh Sleep Quality Index (PSQI).
[1] Yields Total Mood Disturbance Score (TMD).
[2] Height and weight, waist circumference, hip circumference, percent total fat mass, percent total lean mass.
[3] Resting heart rate, systolic blood pressure, diastolic blood pressure.

CHAPTER 4

Stability of Social Jetlag and Sleep Characteristics Over Time: A Prospective Study[1]

[1]McMahon, D.M., Burch, J., Wirth, M.D., Youngstedt, S.D., Hardin, J.W., Hurley, T.G., Blair, S.N., Hand, G.A., Shook, R.P., Drenowatz, C., Hebert, J.R. To be submitted to *Chronobiology International.*

ABSTRACT

Background: Insufficient sleep has been associated with increased risk of many chronic diseases that can take decades to develop. However, few studies have examined the persistence of sleep disruption over time. Armband actigraphy is an objective method of monitoring of an individual's limb movements that yields sleep timing on work and free days, and their difference defines 'social jetlag', a misalignment between internal and social clocks. This prospective investigation examined objectively measured individual sleep characteristics over a two-year period to test the hypothesis that SJL and poor sleep remain stable during this time period.

Methods: Social jetlag [SJL] and sleep measures (total sleep time [TST], sleep onset latency [SOL], wake after sleep onset [WASO]), sleep efficiency [SE]), were derived from physical activity personal armband monitoring among 390 healthy men and women 21-35 years old. Participants wore the armband for a 4-10 day period at 6-month intervals (N=1,431 person-weeks of sleep measurement). The consistency of sleep measures over time was analyzed using generalized linear mixed models (GLMM) for repeated measures. Repeated measures latent class analyses (RMLCA) were then used to identify subgroups among the study participants with adequate or inadequate sleep characteristics over time. These latent groups were then evaluated using GLMM to characterize demographic or other personal characteristics that differed among the subgroups.

Results: Minor changes in mean SJL, chronotype, or TST were observed over time, and no changes in SOL, WASO, or SE were observed during the study period. The RMLCA identified two groups of absolute SJL: low (mean±SE: 0.8±0.6 h, 58%) and high (1.4±0.8, 42%); those with high SJL were employed and had an evening chronotype.

Similarly, two distinct subgroups were observed for SOL, WASO, and SE, with one group consistently exhibiting disrupted sleep over time, and another with a relatively normal sleep pattern; both remaining stable over time. TST had three latent groups with relatively short (5.6±1.0 h, 21%), intermediate (6.5±1.0, 44%) and long (7.3±1.0 h, 36%) durations, all with temporally stable linear trajectories. Subgroups with poor sleep tended to be male, African American, have a lower income, and an evening chronotype relative to those with more normal sleep characteristics.

Conclusions: Objective sleep measures in young adults remained relatively stable over the two-year study period. Sleep disruption symptoms as measured by TST, SOL, WASO and SE, persisted throughout the study. The results suggest that poor sleep can be a chronic condition in certain subgroups, consistent with evidence that sleep disruption contributes to metabolic syndrome, cardiovascular disease, cancer, and other chronic disease risks.

Introduction

Insufficient sleep has been associated with increased risk of major chronic diseases such as cardiovascular disease and hypertension (65, 118), obesity (213), diabetes (120, 214), and cancer (28, 47). The biological processes associated with these impacts may include immunologic, metabolic, and genetic factors (49, 52, 91, 95, 133, 215-217). In order to elicit pathophysiological changes that can lead to chronic disease, sleep has to be disrupted over an extended period of time. However, the temporality of sleep disruption has not been extensively studied. In many longitudinal studies, information about sleep is only obtained at baseline by means of questionnaires, and it is

assumed that self-reported symptoms accurately describe an individual's sleep disturbances, and that they persist over time. However, sleep disruption assessed by self-report can differ from sleep assessed using objective measures (123, 124). For instance, one study among healthy young individuals reported that sleep onset latency was overestimated and frequency of awakening was underestimated using self-reported data (124). In another study, participants with chronic insomnia underestimated their total sleep time and number of awakenings but overestimated sleep onset latency (125). Several longitudinal studies assessed consistency of insomnia and sleep disruption over various periods of time spanning from several months to 20 years (66, 67, 218-226). Presence of insomnia and its subtypes was variable within one year of follow-up (226, 227). Studies with a follow-up of several years showed that insomnia is a fairly persistent condition (66, 67, 218-223, 225), although its patterns may change over time and clinical course of insomnia can exhibit remissions and recurrences (219, 224, 226). Characterizing factors that contribute to the persistence of sleep disruption is important for understanding its role as a chronic disease risk factor.

Only a few studies have investigated the variability of sleep characteristics over prolong periods of time used objective measures such as polysomnography or actigraphy (66-68, 225). In middle-aged people, objective sleep measures, such as sleep duration, efficiency, latency and time in bed showed considerable day-to-day variability, although they were stable during a 1-3 year follow-up (66-68, 225). No comparable studies utilizing objective sleep measures have been conducted among young adults. The importance of such investigations in young adults is based on a high prevalence of

insomnia in the general population and a common knowledge that many chronic diseases that manifest in middle age can take decades to develop.

Most human physiological processes and behaviors exhibit a circadian rhythm (1, 2). Due to variations in intrinsic timing, individuals may be categorized into morning, neutral, or evening chronotypes (3, 4). People with morning chronotypes, the so-called "larks", wake up and go to bed relatively early (between 10 p.m. and midnight), whereas evening chronotypes ("owls"), prefer to wake up and go to bed late (between 1 and 3 a.m) (3). A conflict between this inherent sleep preference and social demands can result in a misalignment in sleep/wake timing, or "social jetlag" (SJL) (6). SJL is calculated as a difference between mid-sleep on free and work days (6); it reflects the potential magnitude and direction of time shift for daily activities as well as physiological and psychological processes (12, 58, 91). Evening chronotypes tend to accumulate a sleep debt during the week for which they try to compensate during the weekend by extending their sleep period. For example, if a person with evening chronotype on work days sleeps between midnight and 6 a.m., his mid-sleep is at 3 a.m. If, on free days, their sleep is extended from midnight until 9 a.m, the mid-sleep is 4:30 a.m, and their SJL is 1 h 30 min. Morning chronotypes, on the contrary, tend to develop sleep debt during the weekend (6). Circadian misalignment resulting from altered sleep/wake timing may lead to metabolic alterations: lipid disregulation, decreased insulin sensitivity, impaired glucose tolerance, altered melatonin and cortisol secretion, and oxidative stress (49, 52, 91). These impacts are commonly observed among shift workers, although some studies suggest that this relationship may extend to populations not involved in shift work, such as those with SJL (12, 25, 37, 47, 49, 58, 107, 228). Although clinically significant cut-

points for SJL have not been established, those with ≥2 h of SJL had shorter sleep duration, higher 5-hour blood cortisol levels, and a higher resting heart rate relative to those with ≤1 h of SJL (49). In addition, those with >2 h of SJL had higher depression scores than those with ≤2 h (37). To date, no prospective studies have examined the persistence of SJL over time.

This study quantitatively assessed sleep and sleep/wake timing among young adults during two years of follow-up to test the hypothesis that SJL and poor sleep remain stable over time. Data were obtained from participants in the Energy Balance Study (EBS), a three-year follow-up study that investigated the effects of energy intake and expenditure on changes in body weight, body composition and health indices among healthy young adults ages 21-34 years (182). This age group is at risk for decreasing metabolic rate and increase in weight and percent of body fat (183, 229) which may lead to development of chronic disease at a later age. Actigraphy measures repeated at 6-month intervals were used to characterize SJL and sleep disturbances at each time point. To assess the consistency of SJL and sleep disturbances over time, generalized linear mixed models were used to evaluate the temporal stability of SJL and each sleep measure, and RMLCA was used to identify subgroups (latent groups) with different sleep trajectories. Finally, the socio-demographic characteristics of each subgroup was described, including the extent to which they are influenced by chronotype.

Methods

Study population

Eligible individuals were 21-35 years of age with no major health conditions or large changes in body composition during the previous six months, and had a BMI of 20-35 kg/m^2 (182). Participants were excluded at baseline if they had systolic blood pressure ≥150 mmHg and/or diastolic blood pressure ≥90 mmHg or a blood glucose level >145 mg/dl as diagnostic criteria for hypertension and diabetes, respectively (182). In 2011, 430 participants residing in the Columbia, SC region were enrolled. After comprehensive baseline assessment, participants were re-examined every 6 months to assess their demographic and anthropometric characteristics, as well as their sleep/wake patterns via armband actigraphy, and to ascertain diet using three 24-hour dietary recalls (2 on random weekdays and one on the weekend). Each participant completed one to five assessments at six-month intervals over the two-year study period (2011-2013). All available repeated measures were used to evaluate the temporal characteristics of SJL and objective sleep measures. Only participants with ≥3 data time points were included in the RMLCA. The study was approved by the University of South Carolina Institutional Review Board, and all participants provided informed consent.

Chronotype, social jetlag and other objective sleep measures

All objective sleep measures were derived from the data collected with a SenseWear® Mini Armband worn by study participants over the triceps muscle of the left arm (184). A micro-electro-mechanical sensor in the armband recorded limb movements at a sampling frequency of 32 times per second averaged over 1-minute intervals. All

participants wore the armband for 7-10 days and kept a log of their activities during periods of non-wear. These activities were matched with the 2011 Compendium of Physical Activity (187) to fill gaps in information on energy expenditure and sleep for non-wear periods (185).

The 1-minute armband data were further summarized using SenseWear Professional® Research Software (Version 7.0, Body Media® Inc.). Demographic information (i.e. age, sex, height, weight and smoking status) was used with proprietary algorithms to calculate objective sleep measures. The armband yields several average night-time sleep measures: sleep onset and wake-up times, TST, SOL, SE and WASO (185). The sleep onset time was defined as the first of three minutes asleep that coincided with ≥10 minutes lying down (185). Wake-up time was defined as the first of 90 consecutive minutes awake following sleep onset (185). TST was defined the sum of all minutes asleep from initiation of the sleep period until wake-up time (185). SE was calculated as a proportion of the total sleep time to the length of the night sleep bout. WASO was calculated as the sum of wake periods of at least two minutes duration between sleep onset and the final wake time (185). All measures were averaged across each data collection period using a minimum of 3 weekdays and one weekend day.

Chronotype was defined as the time of mid-sleep on work days corrected for "make-up sleep" on free days (12). SJL was defined as a difference between unadjusted midpoints of sleep on a weekend and on a week day (12) and modeled as two continuous variables: actual and absolute. It was assumed that free days occurred only on weekends, and rest/activity logs were examined to identify and exclude individuals who did not conform to this pattern (10). Individuals were also excluded from statistical analyses if

their armband data had any of the following characteristics: missing bed- or wake-time, <4 days of data in a given assessment period, missing sleep data on the weekend, extreme or implausible TST values (<4 hours either on weekdays, free days, or on average, TST >11 hours on work days or on average), and when mid-sleep on free days occurred in the afternoon (12). Participants also were excluded if they regularly used sleep promoting medications (≥3 times per week over the counter or prescription), worked night shifts, or traveled across meridians during periods of armband use (12, 230).

Covariates

Estimates of total daily physical activity time were obtained from armband data. Information for the periods of non-wear was supplemented with values for matching activity from the 2011 Compendium of Physical Activity (184). Total daily hours of physical activity were defined as any activity of at least 5 metabolic equivalents. Time napping was obtained from armband data. Dietary information was collected using three 24-hour dietary recalls conducted by phone; two on randomly selected weekdays and one on a weekend. The Nutrient Data System for Research (version 2012: Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota) was used to estimate nutrient and individual food intakes from the dietary recalls. Forty three food parameters and nutrients were further used to calculate a dietary inflammatory index (e-DII) that expresses an inflammatory potential of individual's diet (81). Lower DII scores are anti-inflammatory while the higher scores are more proinflammatory, and the maximum theoretical range is −8.87 to 7.98. To account for individual differences in energy intake, the DII scores were calculated per 1,000 kilocalories (4,184 KJ) (e-DII) as previously described (185).

Statistical analyses

All statistical analyses were performed using SAS 9.4 (Cary, NC). Stability of SJL, absolute SJL, and objective sleep measures (TST, SOL, WASO, SE) over time were analyzed using generalized linear mixed models for repeated measures for which we estimated an unstructured covariance matrix. Time was treated as a main exposure variable (categorical) in crude and adjusted statistical models. The following covariates were considered: sex (male, female), race (European American [EA], African American [AA], Other [Hispanic, Asian, Native American or mixed race]), education (high school graduate/GED some college vs. college ≥ 4 y.), income (<$20,000, 20,000 to <40,000, 40,000 to <60,000, 60,000 to <80,000, ≥80,000), employment (student/other, employed and self employed), marital status (married, single), having children (yes/no), physical activity (h), caffeine intake (g/d), e-DII, napping (yes/no), and season (winter [November-January], spring [February-April], summer [May-July], autumn [August-October]), and current dieting (yes/no). To select potential covariates, bivariate relationships with objective sleep measures were summarized, and variables with p-value <0.2 were selected for inclusion in full statistical models. Manual backwards elimination was used to identify covariates for inclusion in the final model that changed the effect estimate of the main exposure variable by ±10%. Variables that were statistically significant ($p \leq 0.05$) were included in the final model. Each sleep characteristic was modeled separately as a continuous variable. These analyses included 390 participants with valid repeated measures data available (1431 observations). Least squares means of continuous sleep variables, SJL or chronotype at different time points were compared using the F-tests in PROC GLIMMIX.

RMLCA was estimated using PROC TRAJ in SAS to identify latent groups for each continuous variable (absolute SJL, chronotype, TST, SOL, SE, WASO) (202, 203). This analysis assumes a mixture model to define the trajectories of unique subgroups within a population that don't change their group membership over time (204, 205). The best fitting crude model was selected using Bayesian Information Criterion (205). The final selection of the number of latent groups was based on the best model fit and minimum group sizes containing ≥10% of the study population. Analyses for chronotype, TST and SE were adjusted for race (EA vs. AA or Other) and sex, which were assumed not to change over time. WASO was adjusted for race only. Absolute SJL and SOL were not adjusted for race or sex because latent groups were not influenced by these variables. Since the group trajectories for each measure were linear, potential covariates that change over time were not examined. Only participants with at least three assessments during the study period were included into these analyses (n=312). Finally, generalized linear mixed models was estimated to identify demographic and other characteristics that differed among the latent classes for absolute SJL and each of the sleep outcomes.

Results

The final analytical dataset consisted of 390 participants (with a total of 1,431 repeated observations). A majority of the participants had at least three (26%), four (15%), or five (39%) assessments, whereas 11% of participants had one and 10% had two assessments. The average age at baseline was 28±4 years and the sex distribution was approximately equal (51% women, Table 4.1). Most participants were EA (68%) and had at least 4 years of college education (84%). College students comprised 45% of

participants (19% undergraduate, 81% graduate), and another 55% were employed. A majority of participants' annual incomes were below $60,000 (71%). Thirty two percent were married, and 14% had children (Table 4.1).

At baseline, ~50% of participants had ≤1 hour of SJL and another 33% had more than 1 but less than 2 hours, and 17% had ≥2 hours of SJL. At baseline, SJL was moderately correlated with chronotype (Spearman $r=0.42$, $p<0.001$). Adjusted mean SJL values at 12 and 24 months exceeded the baseline average by 6 or 12 minutes, respectively; although the overall linear trend for SJL over two years was not statistically significant (Table 4.2). A 12 min increase was observed for absolute SJL ($p=0.01$, data not shown). TST, SOL, WASO and SE remained stable during the study period, although a minor difference in mean TST value was observed at 12 months relative to 6 months (Table 4.2).

Results from the RMLCA indicated that absolute SJL had 2 latent groups with low (mean±SE, 0.4±0.04 h, 42%) and high (1.4±0.03 h, 58%) values (Figure 1). Minor changes in absolute SJL were observed over time, although neither trajectory departed statistically from linearity. If the RMLCA sample was analyzed using the methods that generated results for Table 4.2, absolute SJL remained stable over the study period ($p=0.1$, data not shown). Three latent groups were apparent for chronotype: early (3.0±0.9 h, 33%), intermediate (4.4±0.9 h, 52%) and late (6.0±1.3 h, 14%). By the end of the study, a 23 minute phase advance was observed in the late chronotype group, although no changes were observed in the other two groups. TST had three latent groups with relatively short (5.6±1.0 h, 21%), intermediate (6.5±1.0, 44%) and long (7.3±1.0 h, 36%) durations, all with temporally stable linear trajectories. SOL was generally low in

this population (<30 minutes for 98% of observations, median: 13 min); two latent groups were identified: low (9.7±1.0 min, 73%) and high (18.3±1.0 min, 27%). Two latent groups were observed for WASO: low (42.1±18.6 min, 77%) and high (90.4±31.0 min, 23%), and for SE: low (74.6±1.0%, 27%) and high SE (85.3±1.0%, 73%). Latent groups for SJL and each sleep parameter all had linear trajectories that remained stable over time (Figure 1).

In bivariate analyses, those in high SJL group were employed and had later chronotypes relative to the low SJL group (Table 4.3). Participants in the short TST group were younger, male, of AA or Other race, had lower incomes, were married, consumed less caffeine, and tended to have a more proinflammatory diet (i.e., higher e-DII scores) compared with those in the intermediate TST group (Table 4.3). Those in the long TST group tended to be female, EA, have higher incomes and no children relative to those with an intermediate TST (Table 4.3). The SOL latent groups differed only by employment status; students had a higher SOL relative to those who were employed (Table 4.4). The two WASO groups differed only by race (Table 4.4); a higher proportion of those with elevated WASO values were of AA or Other race. Among those with low SE, a higher proportion was male, AA or Other race, had lower incomes and consumed less caffeine (Table 4.4). Overall, participants with poor sleep (e.g., high SOL, high WASO, short TST, or low SE) tended to have an evening chronotype.

Discussion

To our knowledge, this is the first study that used actigraphy measures to prospectively describe SJL along with chronotype, TST, SOL, WASO and SE in a non-

clinical population of young adults. The prevalence of SJL in the current study was comparable with previous studies of SJL among adults (≥1 hour: 63-69%, ≥2 h: 26-33%) (12, 49). A majority of participants (58%) was in a latent class with SJL exceeding one hour (mean: 1.4 h at baseline) that increased slightly during the two-year study period (mean: 1.5 h at 24 months). SJL tended to remain stable during the study, whereas by the end of the two-year follow-up, chronotype shifted to an average of 23 minutes earlier. Because the heritability of chronotype may be up to 50% (9), one might not expect such a change within a two year span. However, the phase advance observed in the present study is consistent with results from a large cross-sectional study, which suggested that chronotype gradually becomes earlier after age 20 (88). In a series of large internet surveys, SJL gradually decreased over time between the ages 20 and 35 years and was higher among males than females (6, 12). However, it is unclear whether this represents age-related changes, some form of adaptation, or random variation, or unaccounted cohort effects. Temporal patterns of SJL within individuals have not been reported previously. In the present study, SJL was more common among those with an evening chronotype, and was higher among those who were employed compared to students or those not in the work force. These observations agree with the concept that SJL results from misalignment between an individual's social and biological timing (6). These findings also are consistent with previous observations that young adults with later chronotypes had greater SJL (12, 49, 58). SJL may be associated with increased risk of depression, metabolic syndrome, obesity and cardiovascular disease (12, 37, 49, 58, 92, 107, 228) (12, 37, 49, 58, 92, 107, 228). Thus, understanding the temporal dynamics of

SJL and factors that contribute to increased SJL risk is important for development of disease preventive strategies targeting SJL and the disruption of sleep/wake timing.

To our knowledge, this also is the first longitudinal study to examine objective sleep measures among young adults (21-35 years old) over an extended time period. Poor sleep, defined as a low TST or SE, and elevated SOL or WASO, persisted during the two-year follow-up; 21% of study participants had a short TST (mean: 5.6 h), 32% had elevated WASO (mean: 90 min), 27% had low SE (mean: 75%), and in 27% of participants, SOL was elevated (mean: 19 min). The mean values for sleep parameters in the above groups are consistent with cut-off values for TST, SOL, WASO, and SE that have been used to define disrupted sleep or insomnia in prior studies: <6 h for TST (231-234), ≥12 min for SOL (185, 191), ≥50 min for WASO (185), and <78% (233) or <85% for SE (185). RMLCA was used in this study to define temporal trajectories of chronotype and SJL using objective measures of sleep and sleep/wake timing (34, 38, 235). The characteristics of poor sleep in the latent groups identified by RMLCA were generally consistent with categorizations used previously. For example, mean TST values among latent groups coincided with categories used to define short (≤6 h), intermediate (6-7 h), or long sleep (≥7 h) (61, 65, 231). The mean values for low and high SOL among latent groups in this study (11 and 19 min, respectively) allowed for segregation based on some previously suggested cut-off points (12 min and 15 min) (191, 236), but were lower than the 30-minute value that has been used previously to characterize insomnia (115, 237). Mean values in the low- and high- latent groups for WASO (means: 42 and 91 min, respectively) were both above the previously described cut-point of 30 min for insomnia (115, 237). Finally, the mean values among latent groups of SE (low mean: 75%; high

mean: 85%) identifies two groups that are above and below the previously used cut-point for insomnia of 80% (115, 237); however, they were both below the suggested cut-point from another study (92%) (191).

Some limitations in this study are noteworthy. Information on work schedules was not available for all participants, thus it was assumed that participants worked on weekdays and had free days on weekends. Approximately 45% of participants were students (81% at a graduate level), who typically attend classes and work part-time during the day. A few students may have had evening jobs, although it is unlikely they regularly worked night shifts due to the potential interference with their education. Another potential limitation is that no information was available on alarm clock use on free days. To minimize these potential impacts, participants with extreme or implausible TST values were excluded from the analyses, consistent with prior studies (12, 37). In addition, the generalizability of these results is limited to healthy adults ages 21-35, half of whom were college students and had a relatively low income < $40,000.

A major strength of this study is the use of objective measurements to characterize SJL, chronotype, and sleep, which avoids issues related to self-report of sleep or sleep/wake timing. Armband actigraphy is a valid, non-invasive method for obtaining ‘real-life’ sleep/wake measurements that are compatible with the "gold standard" method of polysomnography (184). Armband data were collected minute-by-minute over several days, and information for non-wear periods was obtained using logs completed by participants. Thus, measurement error was expected to be lower than self report information. Participants did not have any major acute or chronic health conditions that could potentially affect objective sleep measures, and those who regularly used

sleep-promoting medications were excluded. Therefore, confounding by somatic conditions or sleep disorders was unlikely to bias the results.

Studies using multiple cross-sectional analyses suggest that sleep tends to deteriorate with age (total sleep time and SE decrease, WASO and SOL increase) (88, 238). In middle-aged and elderly adults, prospective studies using repeated actigraphic measures of sleep reported that sleep characteristics remained generally stable within a 1 to 2.5-year time frame, although insomnia subtypes changed over time (66, 67, 225, 226). Prospective studies among college students that used questionnaires to assess sleep produced conflicting results with respect to the temporal stability of sleep duration and the number of nocturnal awakenings during a one-semester time frame (126, 127). Among undergraduate college students, sleep duration decreased and the number of awakenings increased as the semester progressed (126). However, in another study, sleep duration and quality increased during a 15-week spring semester (127). In a cohort of 591 young adults surveyed for over 20 years, 35% of those with incident one-month insomnia still had it at the next interview and the cumulative prevalence of one-month insomnia was 20% (220). Forty percent of those with incident insomnia subsequently developed chronic insomnia, and 17-50% of those with insomnia had a subsequent major depressive episode (220). Results of these studies suggest that sleep disruption tends to be persistent, although some inconsistencies have been observed in both younger and older age groups. Whether the observations in the present study correspond to more chronic sleep disruption that extends beyond two years remains to be determined. Given the persistent character of insomnia and other sleep disorders in terms of their reported association with chronic diseases such as depression (37, 220, 239), obesity (213, 240, 241), diabetes (62,

120), hypertension (63, 118, 242), CVD (65) and cancer (28), the identification of susceptible subgroups of young adults with persistent sleep disruption may provide a health benefit to those individuals in terms of chronic disease prevention. The demographic characteristics identified in this study that may contribute to persistent sleep disruption include: male sex, being a student, non-White race, low income, and evening chronotype.

In summary, this study adds to knowledge concerning the temporal patterns of SJL, chronotype, and actigraphic sleep among healthy young adults. Absolute SJL, TST and objectively measured insomnia symptoms remained stable over a two-year span. The findings may contribute to the development of prevention strategies targeting sleep hygiene among young adults to prevent the chronic disease development.

Table 4.1 Demographic characteristics of the Energy Balance Study sample at baseline after basic exclusions

Variable	All Participants (n=390)	Women (n=198)	Men (n=192)
Age (yrs)	27.6±3.8	27.7±3.7	27.4±3.9
Race, n (%)			
European American	264 (68)	131 (66)	133 (70)
African American	47 (12)	31 (16)	16 (8)
Hispanic/Latino	11 (3)	7 (3)	4 (2)
Asian	42 (11)	15 (8)	27 (14)
Native American	12 (3)	8 (4)	4 (2)
Other	14 (3)	6 (3)	8 (4)
Education, n (%)			
HS Graduate/GED Some College	62 (16)	18 (9)	44 (23)
College (4+ years)	328 (84)	180 (91)	148 (77)
Income ($), n (%)			
< 20,000	65 (17)	34 (17)	31 (16)
20,000 to < 40,000	137 (35)	76 (39)	61 (32)
40,000 to < 60,000	74 (19)	37 (19)	37 (19)
60,000 to < 80,000	50 (13)	23 (12)	27 (14)
≥ 80,000	62 (16)	26 (13)	36 (19)
Employment, n (%)			
Employed and self employed	214 (55)	113 (57)	101 (53)
Student/Other[1]	176 (45)	85 (43)	91 (47)
Marital status, n (%)			
Married[2]	178 (46)	90 (45)	88 (46)
Single[3]	212 (54)	108 (55)	104 (54)
Children, age			
<18 years, n (%)			
0	336 (86)	173 (88)	163 (85)
1	29 (7)	13 (7)	16 (8)
≥ 2	24 (7)	11 (5)	13 (7)

[1] Out of work (<1 year), homemaker, unable to work (n=4, 1 %).
[2] Includes members of unmarried couples (n=55, 14 %).
[3] Includes divorced and separated (n=7, 1.7 %).

Table 4.2 Stability of Objective Sleep Measures Over Time (n=390, 1,431 observations)

Sleep measure	Follow-up Time (Months)					F-test, p-value
	Baseline (n=390)	6 (n=341)	12 (n=317)	18 (n=206)	24 (n=177)	
	Mean±SE	Mean±SE	Mean±SE	Mean±SE	Mean±SE	
Social Jet Lag (h)						
Crude	1.2±0.04	1.1±0.04	1.1±0.05	1.2±0.06	1.2±0.06	0.78
Adjusted[1]	0.9±0.05	0.9±0.05	1.0±0.05*	1.0±0.1	1.1±0.1*	0.09
Chronotype (h)						
Crude	4.4±0.1	4.2±0.1*	4.1±0.1*	4.1±0.1*	4.0±0.1*	<0.01
Adjusted[2]	4.4±0.1	4.2±0.1*	4.1±0.1*	4.0±0.1*	4.0±0.1*	<0.01
Total Sleep Time (h)						
Crude	6.6±0.04	6.6±0.04*	6.5±0.04*	6.6±0.05	6.6±0.05	0.10
Adjusted[3]	6.4±0.10	6.5±0.10*	6.3±0.10*	6.4±0.1	6.4±0.10	0.40
Sleep Onset Latency (min)						
Crude	12.9±0.3	13.0±0.3	12.9±0.3	13.8±0.4	12.6±0.4	0.15
Adjusted[4]	12.9±0.3	12.8±0.4	12.7±0.4	13.6±0.4	12.4±0.5	0.16
Wake After Sleep Onset (min)						
Crude	53.8±1.5	54.2±1.6	53.3±1.6	54.0±1.8	51.9±1.9	0.75
Adjusted[5]	61.3±2.2	61.6±2.3	60.7±2.3	61.4±2.4	59.3±2.5	0.77
Sleep Efficiency (%)						
Crude	82.3±0.3	82.4±0.3	82.4±0.4	82.1±0.4	82.6±0.4	0.76
Adjusted[6]	81.2±0.4	81.3±0.4	80.3±0.4	82.0±0.5	81.5±0.5	0.77

Abbreviations: 95%CI - 95% Confidence Interval. Participants with any valid time points (1-5) were included. [1] Adjusted for time, chronotype, race, employment status, and current dieting. [2] Adjusted for age and sex. [3]Adjusted for time, chronotype, gender, race, having children (yes/no), caffeine intake (g/d), napping (yes/no), physical activity (MET-hours, continuous) and season. [4]Adjusted for time, season, income, caffeine, nap, physical activity (MET-hours, continuous). [5] Adjusted for race. [6] Adjusted for race, sex, income, energy-adjusted Dietary Inflammatory Index (continuous), and physical activity (MET-hours, continuous).* $p<0.05$. For absolute SJL time points 12 and 24 months differed from baseline. For Chronotype, every time point was different from the baseline. For TST, time points 6 and 12 m were different from each other.

Table 4.3 Characteristics of Latent Groups within Social Jetlag, Chronotype, and Total Sleep Time (n=312; 1,297 observations)

Variable	Social Jet Lag (h)		p	Total Sleep Time (min)			p
	Low	High		Short	Intermed.	Long	
	Mean±SE	Mean±SE		Mean±SE	Mean±SE	Mean±SE	
	0.8±0.6	1.4±0.8		5.6±0.04	6.5±0.02	7.3±0.03	
	%	%		%	%	%	
Sex							
Male	55	48	0.20	71*	54	35*	<0.01
Female	45	52		29*	46	65*	
Race							
European American	64	68	0.50	27*	71	82	<0.01
African American	12	10		30*	9	2	
Other[1]	24	22		43*	20	16	
Employment							
Student/Other[2]	52	41	0.05	50	46	43	0.70
Employed	48	59		50	54	57	
Income ($)							
< 20,000	19	16	0.80	24*	16	16*	0.02
20,000 to < 40,000	36	38		43*	38	30*	
40,000 to < 60,000	19	19		23*	21	16*	
60,000 to < 80,000	13	14		4*	16	16*	
≥ 80,000	13	13		6*	9	22*	
Marital status							
Married[3]	46	46	0.96	70*	50	50	0.02
Single[4]	54	54		30*	50	50	
Children							
Yes	17	11	0.10	13	18	8*	0.10
No	83	89		87	82	92*	
	Mean±SE	Mean±SE		Mean±SE	Mean±SE	Mean±SE	
Chronotype (h)	3.8±0.1	4.3±0.05	0.01	4.6±0.1*	4.1±0.1	3.9±0.05	<0.01
Age (yrs)	27.8±0.2	27.6±0.1	0.30	27.0±0.2*	28.0±0.2	27.7±0.2	<0.01
Physical activity (h)	2.2±0.1	2.2±0.1	1.00	2.3±0.2	2.3±1.0	2.0±0.1*	0.04
Caffeine (g/d)	109.0±8.6	117.4±6.8	0.50	79.3±11.7*	120.2±7.9	126.5±8.8	<0.01
e-DII	0.4±0.2	0.6±0.1	0.40	1.1±0.2*	0.4±0.1	0.3±0.2	0.01

Abbreviations: SE - standard error, e-DII - energy-adjusted Dietary Inflammatory Index; p - p-value F-test. [1] Hispanic/Latino, Asian, Native American, mixed race. [2] Out of work (<1 year), homemaker, unable to work. [3] Includes members of unmarried couples. [4] Includes divorced and separated. *p<0.05, reference group Intermediate Chronotype.

Table 4.4 Characteristics of latent groups within sleep variables (n=312, N=1,297 observations)

Variable	Sleep Onset Latency		p	Wake After Sleep Onset		p	Sleep Efficiency		p
	Low	High		Low	High		High	Low	
	Mean±SE	Mean±SE		Mean±SE	Mean±SE		Mean±SE	Mean±SE	
	10.8±0.2	19.2±0.3		42.1±0.9	90.7±1.7		85.4±0.1	74.8±0.3	
	%	%		%	%		%	%	
Sex									
Male	49	54	0.50	51	50	0.99	47	60	0.04
Female	51	46		49	50		53	40	
Race									
European American	68	61	0.50	75	36	<0.01	76	40	<0.01
African American	11	11		7	24		7	20	
Other[1]	21	28		18	40		17	40	
Employment									
Student/other[2]	41	58	0.01	43	54	0.10	43	51	0.20
Employed	59	42		57	46		57	49	
Income ($)									
< 20,000	8	17	0.20	16	26	0.10	16	20	0.04
20,000 to < 40,000	33	46		34	45		32	48	
40,000 to < 60,000	22	12		19	19		21	15	
60,000 to < 80,000	14	13		16	5		14	11	
≥ 80,000	13	12		15	5		16	6	
Marital status									
Married[3]	47	42	0.30	47	41	0.40	48	40	0.20
Single[4]	53	58		53	59		52	60	
Children									
Yes	12	18	0.30	14	12	0.60	14	11	0.40
No	88	82		86	88		86	89	
	Mean±SE	Mean±SE		Mean±SE	Mean±SE		Mean±SE	Mean±SE	
Chronotype (h)	4.0±0.04	4.3±0.01	<0.01	4.0±0.04	4.4±0.1	0.01	4.0±0.1	4.4±0.1	<0.01
Age	27.6±0.1	27.8±0.2	0.40	27.7±3.6	27.6±4.2	0.30	27.9±0.1	27.1±0.2	<0.01

Physical activity (h)	2.3±0.1	2.0±0.1	0.10	2.2±0.1	2.1±0.1	0.60	2.2±0.1	2.1±0.1	0.60
Caffeine (g/d)	114.3±3.8	114.2±6.4	0.80	119.9±6.1	94.6±11.2	0.05	124.2±6.2	87.2±10.1	0.01
e-DII	0.5±0.1	0.5±0.2	0.90	0.4±0.1	0.6±0.2	0.40	0.4±0.1	0.6±0.2	0.40

Abbreviations: WASO stands for Wake After Sleep Onset, SE - Standard Error, e-DII - energy-adjusted Dietary Inflammatory Index, p - p-value F-test.

[1] Hispaic/Latino, Asian, Native American, mixed race. [2] Out of work (<1 year), homemaker, unable to work.

[3] Includes members of unmarried couples. [4] Includes divorced and separated

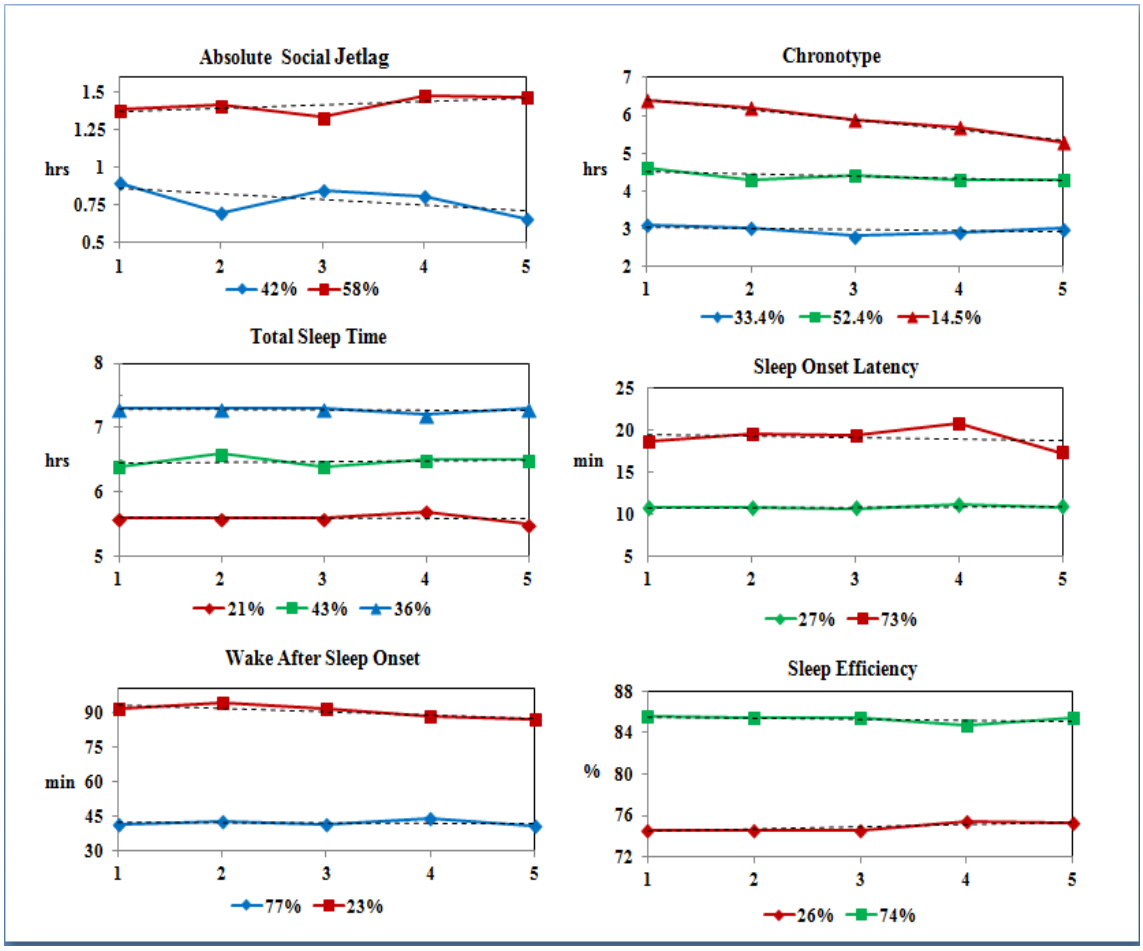

Figure 4.1. Latent group trajectories for Social Jetlag, Chronotype and Objective Sleep Measures at five time points (baseline, 6 m, 12 m, 18 m, and 24 m) obtained with RMLCA analyses (n=312, 1,297 obs.). Only participants with ≥3 time points were included.

CHAPTER 5

Relationships between Social Jetlag, Chronotype and Objective Sleep Characteristics with Anthropometric Indices of Obesity and High Blood Pressure[1]

[1] McMahon, D.M., Burch, J., Wirth, M.D., Youngstedt, S.D., Hardin, J.W., Hurley, T.G., Blair, S.N., Hand, G.A., Shook, R.P., Drenowatz, C., Hebert, J.R. To be submitted to *Chronobiology International*.

ABSTRACT

Background: Chronotype, social jetlag and poor sleep have been associated with increased risk of chronic diseases such as obesity, metabolic syndrome, cardiovascular disease and cancer. Yet, the relationships between these factors have not been extensively investigated in prospective studies.

Methods: Social jetlag [SJL] and objective sleep measures (total sleep time [TST], sleep onset latency [SOL], wake after sleep onset [WASO] and sleep efficiency [SE]) were derived from physical activity personal (armband) monitoring data among 390 healthy men and women 21-35 years of age. Participants wore the armband for 7-10 days at 6-month intervals (1,431 repeated measurements). Generalized linear mixed models with repeated measures (PROC GLIMMIX) were used to analyze relationships between chronotype, absolute SJL, TST, SOL, WASO, SE and anthropometric measures: body mass index [BMI], percent body fat [%BF], waist-to-hip ratio [WHR], waist-to-height ratio [WHtR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]. The relationships between sleep disruption or SJL and indicators of obesity and high blood pressure were evaluated for potential effect modification by chronotype.

Results: Sleep latency ≥12 min was associated with 1.4 times increased odds of high WHtR (odds ratio [OR]=1.4; 95% confidence interval [95%CI]: 1.03-1.84). The odds of high WHtR decreased 0.97 times (95%CI:0.95-0.99) per 1% increase in SE. SJL was correlated with eveningness (Spearman ρ=0.49, $p<0.001$), and evening chronotypes had shorter TST, lower SE and higher WASO compared to those with intermediate chronotypes. Chronotype and absolute SJL were not associated with anthropometric measures. However, chronotype modified relationships between objective sleep measures

and anthropometric measures. Morning chronotypes with short TST (<6 h), low SE (<85%) and large WASO (≥60 min) had increased odds of high %BF, WHR and WHtR, whereas morning chronotypes with longer sleep latencies (≥12 min) had increased odds of high SBP. Among evening chronotypes, shorter sleep (<6 hours) was associated with increased odds of high SBP.

Conclusions: Chronotype and sleep disturbances may work in combination to increase an individual's risk of obesity or elevated blood pressure.

Introduction

In 2013-2014, almost 38% of adults in the United States were obese (243). Obesity is associated with many serious complications such as metabolic syndrome, type 2 diabetes mellitus, arterial hypertension, cardiovascular disease, and cancer (244), some of which develop already in a childhood (183). One modifiable risk factor for obesity is sleep (213, 245). Poor sleep has been associated with has been associated with increased risk of major chronic diseases such as cardiovascular disease and hypertension (65, 118), obesity (213), diabetes (120, 214), and cancer (28, 47).

Sleep timing is related to individual circadian preference and is more efficient when it occurs during preferred times (246). Most physiological and behavioral processes in humans follow ~24-hour internally generated cycles that are synchronized (or entrained) by environmental stimuli, the most important of which is light (1, 2). Due to inherent differences in sleep/wake timing, people tend to be categorized into morning ("larks"), neutral, or evening ("owls") chronotypes (3, 4). For example, people with a morning chronotype go to bed between 10 p.m. and midnight, on average, while evening

chronotypes retire between 1 and 3 a.m on their free days. Individuals with evening chronotypes tend to accumulate sleep debt during the week, for which they try to compensate with a longer sleep during the weekend. Morning chronotypes, on the contrary, tend to develop sleep debt during the weekend (6). Modern life in industrialized countries imposes on individuals multiple work-related and social demands that can come into conflict with the individual's chronotype. This discrepancy (misalignment) between biological preference and social clock is called "social jetlag" (SJL) (6). SJL is calculated as the difference between mid-sleep time on free and work days (6). For instance, if on a work day, a person sleeps from 1 a.m. to 7 a.m. and on free days from 1 a.m. to 9 a.m., his SJL is 1 hour. In experimental studies, circadian misalignment has been implicated in disruption of important physiological processes (92). Social jetlag starts in teenage years and continues throughout working years until retirement and, thus, may affect millions of people in industrialized countries (12). In some reports, SJL has been associated with increased anthropometric indices of obesity, metabolic syndrome, markers of systemic inflammation and mood disorders (12, 37, 49, 58); however, its relationships with other factors, such as sleep disruption and chronotype, that also predispose to chronic disease have not been thoroughly examined.

In several studies, individuals with evening chronotype were more likely to be overweight or obese than those with morning or intermediate chronotypes (33, 53-55); however, not all studies confirmed this association (12, 57). In one study, morning chronotype was associated with increased risk of weight gain (12). Chronotype moderately correlates with social jetlag, especially on work days, and people with evening chronotypes tend to have more social jetlag (6, 12, 37, 49, 58, 236). Chronotype,

in combination with social schedule, can elicit an increase in social jetlag (6, 12). Thus, it is reasonable to hypothesize that social jetlag may mediate the relationship between chronotype and obesity. A study that tested this hypothesis produced conflicting results (56), and most other studies inferred that chronotype, SJL and sleep duration confound each other's associations with anthropometric indexes of obesity and metabolic syndrome (12, 58).

Sleep duration is generally independent from chronotype (88); however, circadian misalignment, a discrepancy between preferred and actual sleep/wake times, is associated with sleep loss (6, 88). Shortened, fragmented or inefficient sleep is associated with increased risk of weight gain and obesity in young adults (54, 213, 232, 234, 236, 240, 247). Poor sleep is prevalent in young adults and tends to be persistent (116, 234, 236, 240, 248, 249). For instance, a recent study showed that in 53% of young adults 19-23 years old, sleep problems persisted over 3 years (249). Our previous research also demonstrated that SJL and poor sleep (low TST, high SOL, high WASO and low SE) derived from armband actigraphy in young adults 21-35 years old remained stable within two year period (submitted). Findings that sleep disruption is associated with chronic diseases warrants further investigation into the interplay between sleep quality, quantity and timing.

The objective of this study was to prospectively examine relationships between SJL, objective sleep measures (TST, SOL, WASO and SE) and anthropometric measures of obesity and high blood pressure (BMI, %BF, WHR, WHtR, SBP, and DBP) among young adults 21-35 years old using a serial cross-sectional study design. This age group is at risk for developing metabolic disturbances that predispose to increased risk for

chronic disease later in life (183, 229). During the last decade, prevalence of obesity in this age group in the United States remained high (30%) (183), a known risk factor for morbidity and premature mortality (250). Adults in this age range also may experience SJL and have persistent poor sleep (116, 234, 236, 240, 248, 249). We hypothesized that young adults with SJL or poor sleep were more likely to be obese, have elevated blood pressure, mood disturbances or elevated stress relative to those without SJL and good sleep, and that such impacts may be modified by chronotype.

Methods

Study population

Eligible individuals were 21-35 years of age, with BMI of 20-35 kg/m^2 , and no major health conditions or large changes in body composition during previous six months (182). In 2011, 430 healthy men and women 21-35 years of age residing in the Columbia, SC region were enrolled. Those who met diagnostic criteria for hypertension and diabetes: systolic blood pressure ≥150 mmHg and/or diastolic blood pressure ≥90 mmHg or a blood glucose level >145 mg/dl, were excluded (182). In 2011, 430 participants residing in the Columbia, SC region were enrolled. After comprehensive baseline assessment, participants were re-examined every 6 months for: socio-demographic and anthropometric characteristics, sleep/wake patterns via armband actigraphy, and diet. During the two-year study period, each participant completed one to five assessments at six-month intervals. The study was approved by the Institutional Review Board at the University of South Carolina, and all study participants provided informed consent.

Chronotype, Social Jetlag and Sleep measures

Objective sleep measures were derived from the data collected using a SenseWear® Mini Armband which participants wore over the triceps muscle of the left arm (184). A micro-electro-mechanical sensor in the armband detects and measures limb movements at a frequency of 32 times per second and data are averaged at 1 minute intervals. The armband data by minute were analyzed using SenseWear Professional® Research Software (Version 7.0, Body Media® Inc.). Demographic information (i.e. age, sex, height, weight and smoking status) was used to customize proprietary algorithms for calculations of objective sleep measures. The participants wore the armband for 7-10 days and kept a log of their activities during periods of non-wear. These activities were matched with the 2011 Compendium of Physical Activity (187) to fill gaps in information on energy expenditure and sleep for non-wear periods (185).

The armband data yields several night-time sleep measures: sleep onset and wake-up times, TST, SOL, WASO and SE (185). The sleep onset time was determined by the first out of three minutes asleep that coincided with ≥ 10 minutes lying down (185). Morning wake-up time was defined by the first out of 90 consecutive minutes awake (185). TST is the sum of all minutes asleep from initiation of the sleep period until wake-up (185). Sleep efficiency was calculated as a proportion of the total sleep time to the length of the night sleep bout. WASO was calculated as the sum of wake periods of at least two minutes long between sleep onset and the final wake time (185). All sleep measures were averaged for each semiannual data collection period for a minimum of 3 weekdays and one weekend day.

Chronotype was measured as the time of mid-sleep on free days corrected for "make-up sleep" on free days (12). Information on work schedule was not collected in this study; it was assumed that free days occurred only on weekends. The sleep logs were examined to find and exclude individuals whose schedules deviated from this pattern (10). Social jetlag (SJL) was calculated as a difference between midpoints of sleep on a weekend and on a week day (unadjusted) (12). The absolute value of SJL was used for all analyses and, referred to as SJL throughout this paper.

Individuals were excluded from statistical analyses if their armband data had the following deficiencies: missing bed time or wake time, <4 days of actigraphy in any given assessment period, missing sleep data on the weekend, extreme or implausible TST values (<4 hours either on week days, free days, or on average, TST >11 hours on work days or on average), and when mid-sleep on free days occurred in the afternoon (12). In addition, participants were excluded from all analyses if they regularly used (≥3 times per week) sleep promoting medications (over the counter or prescription), worked night shifts, or traveled across meridians during periods of armband wear (12, 230).

Anthropometric Outcomes

Height and weight were measured using traditional stadiometer and electronic scales with a precision of 0.1 cm and 0.1 kg, respectively (182). The average of three measurements was used to establish BMI (weight (kg)/height (m^2). Waist and hip circumferences were measured with a calibrated, spring-loaded tape measure. The waist circumference was measured at mid-point between costal margin and iliac crest on the axillary line on both sides of the trunk and 2 cm above the umbilicus (182). Hip

circumference was measured at the level of the greater trochanter, at the widest point. The average of three measurements rounded to 0.1 cm was recorded. Body composition was measured using dual x-ray absorptiometry full body Lunar fan-beam scanner (GE Healthcare model 8743, Waukesha, WI).

Covariates

Total daily physical activity time was obtained from armband data. Information for the periods of non-wear was supplemented with values for matching activity from the 2011 Compendium of Physical Activity (184). Total daily hours of physical activity were defined as any activity of at least 5 metabolic equivalents. Dietary information was collected using three 24-hour dietary recalls conducted by phone; two on randomly selected week days and one on a weekend. To estimate energy, nutrient and individual food intakes from these recalls was used the Nutrient Data System for Research (version 2012: Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota). Forty three food parameters and nutrients were further used to calculate a dietary inflammatory index (DII) that expresses an inflammatory potential of individual's diet (81). Lower DII scores are anti-inflammatory while the higher scores are more proinflammatory, and the maximum theoretical range is −8.87 to 7.98. To account for individual differences in energy intake, the DII scores were calculated per 1,000 kilocalories (4184 KJ) (e-DII) (185).

Statistical Analyses

All statistical analyses were performed using SAS 9.4® (Cary, NC). Continuous actigraphy variables were categorized using previously established cut-points: TST (<6,

6-<7, ≥7 h) (61, 65), SOL (≥12 vs. <12 min) (191), WASO (≥60 vs. <60 min) (119, 188), and SE (<85 vs. ≥85%) (119, 185). Relationships between SJL, chronotype, objective sleep measures (TST, SOL, WASO, SE) and anthropometric measures were analyzed using generalized linear mixed models for repeated measures for which we estimated an unstructured covariance matrix. Odds ratios (OR) and 95% confidence intervals (95%CI) were used to evaluate the relationship between disrupted sleep, individual chronotype, or SJL and measures of obesity, body composition, or blood pressure. BMI was categorized into 2 groups: underweight/normal weight (<25) and overweight/obesity (≥25 B kg/m^2). Sex-specific cut-off points were used to categorize BF% and WHR. Obesity was defined as BF% ≥25% in men and ≥30% in women (98). WHR was dichotomized: <0.95 vs. ≥0.95 in men and <0.80 vs. ≥0.80 in women (200). Waist-to-height ratio was dichotomized as <0.5 vs. ≥0.5 (103). Potential covariates included: age, sex (male, female), race (European American [EA], African American [AA], Other [Hispanic, Asian, Native American and mixed race]), education (high school graduate/GED some college vs. college ≥ 4 y.), income (<$20,000, 20,000 to <40,000, 40,000 to <60,000, 60,000 to <80,000, ≥80,000), employment (student/other vs. employed/self-employed), marital status (married, single), having children (yes/no), physical activity (MET-hours), caffeine intake (g/d), e-DII (≤-1.18, -1.19-≤0.72, 0.73-≤2.10, >2.10), napping (yes/no), and season (winter [November-January], spring [February-April], summer [May-July], autumn [August-October]). The assessment time (one to five at 6-month intervals) was treated as a categorical variable and included in crude and adjusted statistical models. To select potential covariates, bivariate relationships between each sleep measure and the anthropometric outcomes were summarized, and variables with p-value <0.2 were

selected for inclusion in multivariable statistical models. Manual backwards elimination was used to identify covariates that changed an estimate of the main exposure by ±10%. The final model included only confounders detected with 10% rule, or if they were statistically significant ($p \leq 0.05$). Only observations with complete data were included.

Repeated Measures Latent Class Analysis (RMLCA) was estimated using PROC TRAJ in SAS® to identify latent groups for chronotype (morning, intermediate, and evening) over time (202, 203). This analysis assumes a mixture model to define the trajectories of unique subgroups within a population that don't change their group membership over time (204, 205). Assignment to a latent group was based on the highest posterior probability. The best fitting model was selected using Bayesian Information Criterion (BIC) (205) and *a priori* minimum group sizes ≥10% of the study population. RMLCA were adjusted for race (EA vs. AA/Other) and sex, which were assumed not to change over time. Because the group trajectories for all three latent chronotype groups were linear, other potential covariates that change over time were not used to adjust group trajectories. Participants with complete armband data for any available time point were included in these analyses (n=390, 1,431 observations). Generalized linear mixed models were estimated to compare means of SJL, chronotype and each continuous sleep measure between chronotypes using the F-tests in PROC GLIMMIX. The intermediate chronotype was a referent group.

Because chronotype may have several possible roles in how it influences anthropometric outcomes, it was analyzed in several different ways. Chronotype was used as either a continuous or a categorical (RMLCA) independent variable; in the latter analysis, the intermediate chronotype was used as the referent. When examining

relationships between SJL or sleep measures and the anthropometric outcomes, chronotype (continuous) was considered as a potential confounder along with other covariates. The potential role of chronotype as effect modifier was tested using two approaches. In the first approach, an interaction term between chronotype and a main independent variable was added to the multivariable statistical model and assessed using the Wald test. The continuous or categorical version of chronotype that was used for the interaction term was chosen to match the form of the other independent variable. The second approach used stratification of the relationship between absolute SJL, sleep measures and anthropometric outcomes by latent chronotype group.

Results

The final analytical dataset consisted of 390 participants (with a total of 1,431 repeated observations). A majority of the participants had at least three (79%), four (15%) or five (39%) repeated assessments, whereas 10% of participants had two, and 11% had only one assessment. The average age at baseline was 28±4 years, and the sex distribution was approximately equal (51% women) (Table 4.1). Most participants were EA (68%) and had at least 4 years of college (84%). Fifty five percent of participants were employed, and 45% were college students (19% undergraduate, 81% graduate). A majority of participants (71%) had an annual income below $60,000. Thirty two percent of participants were currently married, and 14% had children (Table 4.1). With regard to anthropometric characteristics, 45% of participants were overweight (BMI 25-24.9 kg/m^2, 31%) or obese (BMI≥30, 14%). Among males, 37% had %BF ≥25% and 3% had high WHR (≥0.95). Among females, 71% had %BF ≥30% and 15% had high WHR

(≥0.80). Twenty two percent of participants of both sexes had high WHtR (≥0.5). Systolic blood pressure was elevated (≥120 mmHg) among 59% of participants, including those who met a criterion for hypertension (≥140 mmHg, 11%). Only 23% had elevated DBP (≥80 mmHg), including those with hypertension (≥90 mmHg, 4%).

Chronotype was not associated with any of the anthropometric measures when analyzed as a continuous variable (Table 5.1). The RMLCA identified three latent chronotype groups: morning (mean±SE: 3.0±0.04 h, 32.5% of participants), intermediate (4.4±0.03 h, 53%) and evening (6.1±0.1 h, 14.5%). Chronotype defined by latent group membership was not associated with any anthropometric measures (Table 5.1). At baseline, chronotype was moderately correlated with SJL (Spearman ρ=0.42, $p<0.001$). Compared to participants with an intermediate chronotype (1.2±0.03 h), morning types had significantly less SJL (0.9±0.04, $p<0.001$), whereas those with evening chronotypes had significantly more of SJL (1.5±0.1 h, $p<0.001$) (Table 5.2). The evening types also had significantly shorter TST, lower SE and larger WASO relative to intermediate types (Table 5.2).

Approximately 50% of participants at baseline had more than one hour of SJL (>1 hour and <2 hours: 33%; ≥2 hours: 17%). SJL was not associated with any of the anthropometric measures either before or after stratification by chronotype group (Table 5.3).

Among the sleep measures, SOL, SE, and TST were associated with anthropometric measures. Sleep latency ≥12 min (Ref. <12 min) was associated with an increased odds of elevated WHtR (OR: 1.4, 95%CI: 1.03-1.84, Table 5.4). The odds of high WHtR decreased 0.97 times (95%CI:0.95-0.99) per 1% increase in SE (Table 5.4).

The odds of elevated SBP decreased 0.8 times (95%CI: 0.66-0.97) per 1 hour increase in TST; although it was not confirmed in adjusted analysis (Table 5.4). Chronotype continuous) was not included into the final models due to the negative tests for confounding (10% rule).

Stratification by latent chronotype group indicated that morning types who also had short TST (<6 h), elevated WASO (≥60 min) or low SE (<85%) were more likely to have increased %BF, WHR and WHtR (Table 5.5). Participants with sleep latency ≥12 min who also had a morning chronotype were 1.9 times more likely to have elevated SBP (95%CI: 1.15-3.16, $p_{interaction}$=0.02, Table 5.5). Among the late chronotypes, the odds of high SBP were 2.6 times greater among those who also had short TST (<6 h, 95%CI: 1.08-6.40, $p_{interaction}$=0.74, Table 5.5). Elevated WASO (≥60 min) was associated with an increased odds of high DBP only among those with an intermediate chronotype (OR: 1.7, 95%CI: 1.05-2.71, $p_{interaction}$=0.10, Table 5.5). Results obtained when the data were analyzed using sleep measures as continuous variables were generally consistent with those obtained using categorical sleep variables. For example, among morning types, the odds of an elevated WHR or WHtR decreased with each 1% increase in SE (OR=0.91; 95%CI: 0.85-0.98, $p_{interaction}$=0.004 and OR=0.95; 95%CI: 0.91-0.98, $p_{interaction}$=0.14, Table 3). Measures of chronotype, SJL or sleep were not associated with BMI.

Discussion

To the author's knowledge, this is the first study to use repeated actigraphy measures to examine relationships between chronotype, SJL, and objective sleep measures to characterize longitudinal associations with anthropometric indices of obesity

or hypertension. This study revealed that among healthy adults ages 20-35 years, disrupted sleep was associated with %BF and WHtR, whereas SJL and chronotype had no direct association with the anthropometric outcomes. These observations are consistent with previous studies that found an association between sleep disruption and risk of weight gain or obesity in young adults (213, 231, 232, 234, 236, 240, 241). In the current study, measures of body composition and abdominal adiposity (%BF, WHR, WHtR) tended to be most strongly associated with sleep measures, whereas the results for BMI and sleep measures did not indicate an association. In this study, those with larger SOL were predisposed to elevated WHtR, whereas increases in SE and sleep duration were protective. Short TST was associated with increased WHR, although only among morning types. Others have reported that short sleep duration was associated with increased waist circumference among women, although the participants' chronotypes were not evaluated (233, 241). Disrupted sleep in the current study, defined as short TST, high SOL, high WASO, or low SE, was not associated with BMI, whereas relationships with indices of %BF, WHR and WHtR were observed. The reasons for these discrepancies are uncertain but may be due to minor differences in the accuracy of the indicator. For example, BMI likely underestimates obesity among those with BMI <30 kg/m^2 (251), or overestimates among college athletes (252) relative to percent body fat. Most studies found that evening types were more likely to be obese compared to morning types (33, 51, 53-55). However, one large cross-sectional study reported that morning circadian preference was associated with increased BMI (12). In the present study, the lack of association between chronotype and BMI is in agreement with findings reported in another study (58).

Although chronotype had no direct associations with outcomes in the present study, relationships between sleep disturbances and the anthropometric measures were modified by chronotype. Morning types with disrupted sleep, characterized as either short TST, elevated WASO, or low SE, had increased odds of increased %BF, WHR and WHtR. This finding is relatively novel since most previous studies investigated the effects of chronotype or sleep on obesity independently (33, 51, 53-55, 213, 231-234, 236, 240, 241). Some studies adjusted for the effects of chronotype and sleep duration while examining the relationship between absolute SJL and BMI, percent fat mass, waist circumference, and obesity (12, 58). Increase in SJL or morningness, or decrease in sleep duration were independently associated with increased odds of being overweight or obese while adjusted for the other two variables (12). In the same study, among people with normal weight, chronotype and sleep duration were associated with BMI while SJL was not. Among overweight or obese people, SJL and decrease in sleep duration were associated with increase in BMI, and chronotype was not a significant predictor. In another study, SJL was associated with increase in BMI, fat mass, waist circumference and obesity while chronotype and sleep duration in the same statistical model were not associated with those measures (58). It is not clear why measures of disrupted sleep were associated with increases in anthropometric indexes of obesity predominantly among morning types. It suggests that a morning circadian preference increases vulnerability to the detrimental effects of sleep disturbance, and that the effect is linked to physiological processes controlling fat deposition. In another study, morning chronotypes had higher baseline and postprandial total cholesterol, lower low density lipoprotein and a higher adiponectin compared to intermediate or evening chronotypes (46). In the same study,

participants with morning chronotypes had higher baseline glucose levels and the greatest increases in postprandial blood glucose levels compared to other chronotypes (46). Others have observed that morning chronotypes had a higher cortisol awakening response relative to evening types (48, 253) and a stronger homeostatic response to sleep fragmentation than evening types (254). Morningness has been associated with decreased quality of sleep, problems maintaining sleep, and early awakenings relative to eveningness (45), which may be related to the tendency towards shift work intolerance that has been observed in this group (13, 14).

In the current study, an interaction between sleep disturbances and chronotype also was observed in relation to arterial hypertension. Among evening chronotypes, those with TST <6 hours were 2.6 times more likely to have elevated SBP compared to those who slept 6 to less than 7 hours. In another study that examined blood pressure, there was no statistically significant interaction between sleep duration and chronotype; although TST ≤ 6 hours and evening chronotype were independently associated with increased risk of arterial hypertension (46). Evening chronotypes tend to have shorter sleep duration on work days relative to other chronotypes (88, 255). Poor sleep also is common among evening types (255, 256), consistent with results from the present study (236). Short or fragmented sleep may initiate a neuroendocrine stress response, leading to increased activity of the sympathoadrenal and hypothalamo-pituitary axis, which in turn can increase heart rate, blood pressure, increase evening cortisol, impair glucose metabolism, and lead to abdominal adiposity (257-259).

Absolute SJL was not associated with any of the anthropometric indices of obesity in this study. In prior cross-sectional studies, SJL was associated with increased

BMI, fat mass, and waist circumference (12, 58, 228). In one study, SJL predicted increases in BMI only among those who were already overweight or obese (12). It is not clear why results from the present study were inconsistent with those of others. This present study used quantitative actigraphic armband data to characterize SJL, whereas others typically used self-report information to ascertain sleep/wake timing. The current study had fewer individuals with elevated absolute SJL relative to other studies (>1h 51% vs. 63-69%, ≥2h 16% vs. 26-30%, respectively) where the majority of participants were Caucasians in the age range 15-65 y. (12, 49, 58). Other studies asserted that SJL, chronotype, and sleep duration confound relationships of one another with obesity measures (12, 58, 228). It is plausible that the relationships between these variables are more complex. For instance, it has been proposed that SJL may mediate rather than confound the relationship between chronotype and anthropometric measures (49, 56). If this is the case, adjustment for mediator may introduce bias. Since in this study, neither chronotype nor SJL were associated with anthropometric outcomes, it was not possible to conduct a mediation analyses to test this hypothesis. Participants of this study did not have any major acute or chronic health conditions that could potentially affect sleep, and those who regularly used sleep promoting medications, both over the counter and prescription, were excluded. Therefore, confounding by somatic conditions or sleep disorders was unlikely to bias the results. Alternatively, the study population was relatively young and healthy, thus they may have been more resilient to the potential effects of sleep disturbances or changes in sleep/wake timing on measures of total and central obesity and blood pressure.

This study also has a few noteworthy limitations. Since work schedules were not available for all participants, it was assumed that they only worked on weekdays and were free on weekends. Approximately 45% of study participants were graduate students who typically attend classes and work part-time during the day. Regular night work may be less likely in this population since it would potentially interfere with coursework. In any case, to diminish the possible influence of shift work on the study results, participants with extreme or implausible sleep schedules (TST values <4 hours either on week days, free days, or on average, or mid-sleep time in the afternoon) were excluded (12, 37, 230, 255). Also, no information was available on alarm clock use on free days. Finally, the generalizability of these results is limited to healthy adults ages 21-35, half of whom were college students with relatively low incomes (<$40,000).

The main strength of this study was the use of actigraphic measurements to define SJL, chronotype, and sleep disruption, which avoids issues inherent to self-report data. Armband actigraphy is a convenient, non-invasive and relatively inexpensive method for quantifying sleep that is comparable with the "gold standard" method of polysomnography (184). The armbands provided minute-by-minute measurements over several days, and information for non-wear periods was obtained by inspecting the data and using logs completed by participants. Other study strengths included: the use of a repeated measures design to increase statistical power, the use of gender-specific cut-points for obesity measures, which decreases potential misclassification of outcomes (98, 99, 103, 200), and a statistical modeling strategy that accounted for possible temporal changes and correlated data within individuals. The RMLCA was used to categorize participants into latent chronotype groups based on individual trajectories over time. This

'data-driven' approach provided clear contrasts among those with different chronotypes and served as a robust method for defining chronotype groups (3, 37, 235). The prevalence of early (32.5%), intermediate (53%) and late (14.5%) chronotype groups using RMLCA in this study was comparable with chronotype distributions in the same age range (23-35 y.) from larger cross-sectional surveys (255, 256).

In summary, this study found that disrupted sleep (SOL, SE, TST) had a modest association with central obesity and high SBP, whereas crude associations between short TST and SBP were not statistically significant after adjustment for confounding. A somewhat unexpected finding was that neither chronotype nor SJL were independently associated with the anthropometric outcomes measured. However, chronotype tended to modify the relationship between disrupted sleep and the anthropometric measures. Those with poor sleep and a morning chronotype were more likely to have excess body fat and central obesity. Evening chronotypes who slept <6 hours had increased odds of elevated SBP. The complex relationships between sleep, chronotype, SJL and anthropometric indices of obesity and hypertension deserve careful examination in the future studies.

Table 5.1 Relationships between Chronotype and Anthropometric Characteristics

Anthropometric characteristic	Model	Chronotype (continuous)		Chronotype group (ref. Intermediate)		
		OR (95% CI)	p-value	Early OR (95% CI)	Late OR (95% CI)	p-value
Body Mass Index (kg/m^2)	Crude	0.91 (0.79-1.06)	0.24	1.56 (0.81-2.98)	0.95 (0.39-2.28)	0.36
	Adjusted[1]	0.86 (0.76-1.03)	0.12	1.49 (0.80-2.78)[3]	1.22 (0.50-2.97)[3]	0.45
Percent body fat	Crude	1.01 (0.86-1.17)	0.94	0.67 (0.35-1.30)	0.45 (0.18-1.12)	0.17
	Adjusted[1]	1.11 (0.94-1.31)	0.22	0.77 (0.40-1.50)[4]	1.41 (0.54-3.69)[4]	0.48
Waist-to-hip ratio	Crude	0.83 (0.68-1.01)	0.07	1.24 (0.64-2.44)	0.58 (0.20-1.66)	0.38
	Adjusted[2]	0.86 (0.69-1.07)	0.17	1.18 (0.56-2.48)[5]	1.66 (0.46-6.06)[5]	0.71
Waist-to-height ratio	Crude	0.96 (0.82-1.13)	0.64	1.30 (0.67-2.52)	0.70 (0.30-1.98)	0.55
	Adjusted[2]	0.98 (0.83-1.17)	0.86	1.38 (0.70-2.73)[2]	1.36 (0.50-3.72)[2]	0.60
Systolic BP (mmHg)	Crude	1.00 (0.90-1.11)	0.90	1.21 (0.81-1.81)	1.81 (1.04-3.13)	0.10
	Adjusted[1]	0.96 (0.87-1.07)	0.47	1.16 (0.79-1.72)[1]	1.10 (0.63-1.90)[1]	0.74
Diastolic BP (mmHg)	Crude	1.07 (0.96-1.20)	0.22	0.95 (0.62-1.44)[1]	1.83 (1.06-3.16)[1]	0.06
	Adjusted[1]	1.04 (0.93-1.16)	0.49	0.89 (0.59-1.34)	1.19 (0.68-2.07)	0.61

Abbreviations: BP - blood pressure, OR - odds ratio, 95%CI - 95% confidence interval.
Cutoff points for anthropometric characteristics: Body Mass Index (≥25 vs. <25 kg/m^2), percent body fat (males ≥25 vs. <25 %, females ≥30 vs. <30 %), waist-to-hip ratio (males ≥0.95 vs. <0.95, females ≥0.8 vs. <0.8), waist-to-height ratio (≥0.5 vs. <0.5), systolic BP (≥120 vs. <120 mmHg), diastolic BP (≥ 80 vs.<80 mmHg).
[1] Adjusted for time, sex, physical activity (MET-hours, continuous). [2] Adjusted for time, age, sex, physical activity (MET-hours, continuous). [3] Adjusted for time, sex, physical activity (MET-hours, continuous) and income. [4] Adjusted for time, sex, race and physical activity (MET-hours, continuous). [5] Adjusted for time, age, sex, race, physical activity (MET-hours, continuous) and employment status.

Table 5.2 Objective Sleep Characteristics by Latent Chronotype Group (n=390, 1,431 observations)

Variable	Early 32.5% Mean±SE	Intermediate 53% Mean±SE	Late 14.5% Mean±SE	F-test, p-value
Chronotype (h)	3.0±0.04*	4.4±0.03	6.1±0.1*	<0.01
Total Sleep Time (h)[1]	6.4±0.1	6.4±0.1	6.1±0.1*	0.01
Total Sleep Time on work days (h)[2]	6.3±0.1	6.3±0.1	6.1±0.1*	0.06
Sleep latency (min)[2]	11.1±0.04	11.6±0.03	10.6±0.1	0.35
Sleep efficiency (%)[3]	81.4±0.5	81.3±0.5	78.8±0.8*	0.01
WASO (min)[4]	58.5±2.4	58.4±2.0	66.1±3.4*	0.11
Absolute SJL (h)[5]	0.9±0.04*	1.2±0.03	1.5±0.1*	<0.01

Abbreviations: WASO - Wake After Sleep Onset, SJL - Social Jetlag, 95%CI - 95% confidence interval. Partial F-test in GLIMMIX with repeated measures and unstructured covariance matrix.
*p<0.05 (Reference group - Intermediate chronotype).
[1] Adjusted for time, sex, race, having children, employment status, physical activity and caffeine intake. [2] Adjusted for time, sex, race, employment status, physical activity (MET-hours, continuous). [3] Adjusted for time, sex, race, employment status and caffeine intake. [4] Adjusted for time, sex and having children.
[5] Adjusted for time and employment status.

Table 5.3 Relationships between Absolute Social Jetlag (continuous) and Anthropometric Characteristics

Anthropometric characteristic	Chronotype group	OR (95% CI)	F-test	p interaction
Body Mass Index[1] (kg/m^2)	All	0.93 (0.73-1.16)	0.71	0.82
	Early	0.96 (0.61-1.51)	0.85	
	Intermediate	0.98 (0.72-1.34)	0.90	
	Late	0.98 (0.57-1.69)	0.95	
Percent body fat[1]	All	0.90 (0.70-1.15)	0.41	0.91
	Early	0.82 (0.51-1.32)	0.41	
	Intermediate	0.96 (0.67-1.36)	0.81	
	Late	0.77 (0.40-1.50)	0.44	
Waist-to-hip ratio[1]	All	0.81 (0.59-1.12)	0.20	0.29
	Early	0.78 (0.43-1.42)	0.41	
	Intermediate	0.73 (0.46-1.14)	0.17	
	Late	1.58 (0.64-3.90)	0.31	
Waist-to-height ratio[2]	All	1.00 (0.77-1.29)	0.98	0.89
	Early	1.04 (0.57-1.91)	0.90	
	Intermediate	1.01 (0.71-1.43)	0.96	
	Late	0.99 (0.53-1.85)	0.98	
Systolic BP[1] (mmHg)	All	1.12 (0.95-1.31)	0.19	0.37
	Early	0.92 (0.67-1.25)	0.59	
	Intermediate	1.31 (1.03-1.67)	0.03	
	Late	0.99 (0.69-1.42)	0.95	
Diastolic BP[1] (mmHg)	All	1.02 (0.86-1.21)	0.83	0.38
	Early	0.89 (0.62-1.27)	0.51	
	Intermediate	1.04 (0.81-1.33)	0.78	
	Late	1.08 (0.74-1.57)	0.69	

Abbreviations: BP - blood pressure, OR - odds ratio, 95%CI - 95% confidence interval
Cutoff points for anthropometric characteristics: Body Mass Index (≥25 vs. <25 kg/m^2), percent body fat (males ≥25 vs. <25 %, females ≥30 vs. <30 %), waist-to-hip ratio (males ≥0.95 vs. <0.95, females ≥0.8 vs. <0.8), waist-to-height ratio (≥0.5 vs. <0.5), systolic BP (≥120 vs. <120 mmHg), diastolic BP (≥80 vs. <80 mmHg).
[1] Adjusted for time, sex and physical activity (MET-hours, continuous). [2] Adjusted for time, age, sex and physical activity (MET-hours, continuous).

Table 5.4. Relationships between Sleep Measures and Anthropometric Measures						
Anthropometric characteristic	**Model**	**Total Sleep Time (ref. 6-<7 h)**		**Sleep Efficiency**	**Sleep Latency**	**Wake After Sleep Onset**
		OR (95%CI)	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Body Mass Index (kg/m^2)		<6 h	≥7 h	<85 vs. ≥85%	≥12 vs. <12 min	≥60 vs. <60 min
	Crude	1.28 (0.77-2.10)	1.01 (0.65-1.57)	1.03 (0.68-1.54)	1.06 (0.72-1.55)	1.04 (0.67-1.60)
	Adjusted	1.30 (0.77-2.19)[1]	0.87 (0.55-1.37)[1]	0.96 (0.64-1.48)[1]	0.99 (0.67-1.45)[2]	0.97 (0.63-1.51)[1]
		continuous		continuous	continuous	continuous
	Crude	0.88 (0.67-1.14)		1.00 (0.97-1.03)	1.01 (0.98-1.05)	1.00 (0.99-1.01)
	Adjusted	0.81 (0.62-1.06)[1]		1.01 (0.97-1.04)[1]	1.00 (0.97-1.04)[2]	1.00 (0.99-1.01)[1]
Percent body fat		<6 h	≥7 h	<85 vs. ≥85%	≥12 vs. <12 min	≥60 vs. <60 min
	Crude	0.88 (0.53-1.49)	1.02 (0.64-1.64)	0.98 (0.65-1.48)	1.41 (0.94-2.10)	1.35 (0.86-2.14)
	Adjusted	1.00 (0.57-1.77)[3]	0.75 (0.45-1.24)[3]	0.95 (0.60-1.51)[4]	1.41 (0.91-2.16)[3]	1.31 (0.80-2.14)[3]
		continuous		continuous	continuous	continuous
	Crude	1.07 (0.81-1.41)		0.97 (0.94-1.00)	1.04 (1.00-1.07)	1.01 (1.00-1.02)
	Adjusted	0.83 (0.62-1.12)[3]		1.02 (0.93-1.01)[4]	1.03 (1.00-1.07)[3]	1.01 (1.00-1.02)[3]
Waist-to-hip ratio		<6 h	≥7 h	<85 vs. ≥85%	≥12 vs. <12 min	≥60 vs. <60 min
	Crude	1.16 (0.62-2.18)	1.17 (0.66-2.09)	1.22 (0.72-2.08)	1.25 (0.76-2.06)	1.31 (0.76-2.24)
	Adjusted	1.34 (0.68-2.63)[5]	0.98 (0.53-1.80)[5]	1.20 (0.68-2.12)[5]	1.23 (0.73-2.08)[5]	1.23 (0.69-2.18)[3]
		continuous		continuous	continuous	continuous
	Crude	1.09 (0.79-1.52)		0.98 (0.94-1.02)	1.00 (0.96-1.04)	1.00 (1.00-1.01)
	Adjusted	0.93 (0.63-1.31)[5]		0.98 (0.94-1.03)[5]	0.97 (0.94-1.03)[5]	1.00 (0.99-1.01)[3]
Waist-to-height ratio		<6 h	≥7 h	<85 vs. ≥85%	≥12 vs. <12 min	≥60 vs. <60 min
	Crude	1.16 (0.62-2.18)	1.17 (0.66-2.09)	1.14 (0.89-1.47)	1.29 (1.01-1.65)	1.15 (0.71-1.87)
	Adjusted	1.58 (0.88-2.83)[5]	0.76 (0.45-1.30)[5]	1.16 (0.86-1.55)[5]	1.37 (1.03-1.84)[6]	1.30 (0.96-1.75)[5]
		continuous		continuous	continuous	continuous
	Crude	0.83 (0.62-1.12)		0.98 (0.06-1.00)	1.03 (1.01-1.04)	1.00 (1.00-1.01)
	Adjusted	0.76 (0.56-1.04)[5]		0.97 (0.95-0.99)[5]	1.02 (1.00-1.04)[6]	1.00 (1.00-1.01)[5]
Systolic BP (mmHg)		<6 h	≥7 h	<85 vs. ≥85%	≥12 vs. <12 min	≥60 vs. <60 min
	Crude	1.36 (0.95-1.96)	0.90 (0.64-1.25)	0.98 (0.96-1.01)	1.13 (0.85-1.50)	1.32 (0.96-1.82)
	Adjusted	1.26 (0.87-1.81)[3]	0.95 (0.68-1.33)[3]	1.15 (0.85-1.55)[3]	1.05 (0.79-1.40)[3]	1.31 (0.95-1.79)[5]

		continuous		continuous	continuous	continuous
	Crude	0.80 (0.66-0.97)		0.98 (0.95-1.00)	1.02 (0.99-1.04)	1.00 (1.00-1.01)
	Adjusted	0.86 (0.71-1.04)[3]		0.98 (0.96-1.01)[3]	1.01 (0.98-1.03)[3]	1.00 (1.00-1.01)[5]
		<6 h	≥7 h	<85 vs. ≥85%	≥12 vs. <12 min	≥60 vs. <60 min
Diastolic BP (mmHg)	Crude	1.26 (0.85-1.86)	1.18 (0.83-1.70)	1.12 (0.81-1.54)	1.16 (0.86-1.58)	1.24 (0.89-1.73)
	Adjusted	1.18 (0.80-1.75)[3]	1.28 (0.89-1.84)[3]	1.04 (0.75-1.43)[3]	1.08 (0.79-1.46)[3]	1.23 (0.88-1.73)[5]
		continuous		continuous	continuous	continuous
	Crude	0.86 (0.70-1.05)		0.97 (0.95-1.00)	1.02 (0.99-1.04)	1.00 (1.00-1.01)
	Adjusted	0.92 (0.75-1.12)[3]		0.98 (0.96-1.01)[3]	1.01 (0.98-1.03)[3]	1.00 (1.00-1.01)[5]

Abbreviations: WASO - Wake After Sleep Onset, BP - blood pressure, OR - odds ratio, 95%CI - 95% confidence interval.
Cutoff points for anthropometric characteristics: Body Mass Index (≥25 vs. <25 kg/m^2), percent body fat (males ≥25 vs. <25 %, females ≥30 vs. <30 %), waist-to-hip ratio (males ≥0.95 vs. <0.95, females ≥0.8 vs. <0.8), waist-to-height ratio (≥0.5 vs. <0.5), systolic BP (≥120 vs. <120 mmHg), diastolic BP (≥80 vs. <80 mmHg).
[1] Adjusted for time, sex, income and physical activity. [2] Adjusted for time, sex, employment status and physical activity. [3]Adjusted for time, sex, physical activity. [4] Adjusted for time, sex, physical activity and sleep latency.[5] Adjusted for time, age, sex and physical activity.
[6] Adjusted for time, age, sex, race and physical activity.

Table 5.5 Relationships between Sleep Measures and Anthropometrics stratified by Latent Chronotype Group

Anthropometric characteristic	Chronotype group	Total Sleep Time (ref. 6-<7 h)		Sleep Efficiency	Sleep Latency	WASO
		<6 h	≥7 h	<85% vs. ≥85%	≥12 vs. <12 min	≥60 vs. <60 min
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Body Mass Index (kg/m^2)	Early	0.98 (0.34-2.82)[1]	1.01 (0.42-2.44)[2]	1.12 (0.52-2.43)[2]	1.17 (0.55-2.51)[3]	0.88 (0.37-2.10)[1]
	Intermediate	1.63 (0.79-3.37)[1]	0.81 (0.45-1.47)[1]	0.99 (0.57-1.71)[2]	1.04 (0.62-1.75)[3]	1.26 (0.69-2.29)[1]
	Late	1.31 (0.33-5.27)[1]	1.77 (0.28-11.18)[1]	0.60 (0.17-2.11)[2]	1.26 (0.43-3.74)[3]	1.38 (0.39-4.86)[1]
$p_{interaction}$		0.99		0.69	0.97	0.32
Percent body fat	Early	0.88 (0.30-2.57)[2]	0.69 (0.27-1.73)[2]	1.22 (0.53-2.84)[4]	1.73 (0.81-3.72)[2]	3.43 (1.35-8.72)[2]
	Intermediate	0.83 (0.37-1.86)[2]	0.79 (0.40-1.56)[2]	0.80 (0.43-1.50)[4]	1.33 (0.73-2.41)[2]	0.71 (0.37-1.38)[2]
	Late	1.23 (0.28-5.48)[2]	0.59 (0.09-3.79)[2]	0.68 (0.14-3.30)[4]	1.18 (0.29-4.82)[2]	1.38 (0.30-6.26)[2]
$p_{interaction}$		0.92		0.64	0.84	0.03
Waist-to-hip ratio	Early	3.91 (1.19-12.84)[5]	1.39 (0.42-4.54)[5]	3.38 (1.07-10.69)[5]	2.13 (0.83-5.47)[2]	3.72 (1.38-10.07)[2]
	Intermediate	0.66 (0.25-1.78)[5]	0.82 (0.37-1.80)[5]	0.95 (0.46-1.95)[5]	1.06 (0.54-2.10)[2]	0.67 (0.30-1.51)[2]
	Late	2.01 (0.19-21.28)[5]	1.36 (0.16-11.59)[5]	0.20 (0.03-1.30)[5]	0.19 (0.03-1.20)[2]	0.42 (0.06-2.90)[2]
$p_{interaction}$		0.15		0.03	0.27	0.01
Waist-to-height ratio	Early	1.59 (0.47-5.39)[5]	0.60 (0.21-1.72)[5]	1.89 (1.10-3.25)[5]	1.63 (0.94-2.84)[6]	2.21 (1.27-3.84)[5]
	Intermediate	1.76 (0.79-3.84)[5]	0.85 (0.42-1.70)[5]	0.87 (0.58-1.30)[5]	1.44 (0.96-2.18)[6]	0.81 (0.53-1.24)[5]
	Late	1.05 (0.22-5.09)[5]	1.65 (0.26-10.31)[5]	0.95 (0.39-2.32)[5]	0.87 (0.37-2.09)[6]	1.28 (0.55-2.94)[5]
$p_{interaction}$		0.74		0.05	0.13	0.007
Systolic BP, mmHg	Early	0.70 (0.36-1.38)[5]	0.65 (0.37-1.16)[5]	1.05 (0.63-1.75)[2]	1.90 (1.15-3.16)[2]	1.19 (0.67-2.09)[5]
	Intermediate	1.45 (0.85-2.46)[5]	1.09 (0.68-1.75)[5]	1.24 (0.81-1.89)[2]	0.90 (0.59-1.35)[2]	1.38 (0.87-2.18)[5]
	Late	2.63 (1.08-6.40)[5]	2.31 (0.74-7.27)[5]	0.96 (0.41-2.22)[2]	0.63 (0.29-1.35)[2]	1.21 (0.55-2.66)[5]
$p_{interaction}$		0.74		0.95	0.02	0.93
Diastolic BP, mmHg	Early	0.83 (0.38-1.81)[2]	1.51 (0.79-2.90)[2]	0.67 (0.38-1.20)[2]	0.83 (0.47-1.45)[2]	0.94 (0.50-1.78)[5]
	Intermediate	1.44 (0.81-2.54)[2]	1.46 (0.88-2.40)[2]	1.41 (0.90-2.22)[2]	1.40 (0.90-2.16)[2]	1.68 (1.05-2.71)[5]
	Late	1.15 (0.49-2.72)[2]	0.63 (0.20-2.01)[2]	0.72 (0.30-1.74)[2]	0.79 (0.36-1.73)[2]	0.73 (0.32-1.64)[5]
$p_{interaction}$		0.50		0.13	0.33	0.10

Abbreviations: WASO - Wake After Sleep Onset, BP - blood pressure, OR - odds ratio, 95%CI - 95% confidence interval.
$p_{interaction}$: p-value for the interaction term between a sleep variable and chronotype group in adjusted statistical model.

Cutoff points for anthropometric characteristics: Body Mass Index (≥25 vs. <25 kg/m^2), percent body fat (males ≥25 vs. <25%, females ≥30 vs. <30%), waist-to-hip ratio (males ≥0.95 vs. <0.95, females ≥0.8 vs. <0.8), waist-to-height ratio (≥0.5 vs. <0.5), systolic BP (≥120 vs. <120 mmHg), diastolic BP (≥ 80 vs.<80 mmHg).

[1] Adjusted for time, sex, income and physical activity. [2]Adjusted for time, sex, physical activity (MET-hours, continuous). [3] Adjusted for time, sex, employment status and physical activity (MET-hours, continuous). [4]Adjusted for time, sex, physical activity (MET-hours, continuous) and sleep latency. [5]Adjusted for time, age, sex and physical activity (MET-hours, continuous).[6] Adjusted for time, age, sex, race and physical activity (MET-hours, continuous).

CHAPTER 6

Diet-Related Inflammatory Index and Prostate Cancer Risk in the California Men's Health Study[1]

[1] McMahon, D.M., Burch, J., Hebert, J.R., et al. To be submitted to *Urology*.

ABSTRACT

Background: Recent studies suggest that the inflammatory potential of individuals' diets may be associated with increased risk of Prostate Cancer (PrCA) whose incidence and mortality vary by race and socioeconomic status.

Methods: The association between energy-density Dietary Inflammatory Index (e-DII) and incident PrCA was examined among participants in the California Men's Health Study (CMHS) (N=40,161). The men were 45-69 years old at recruitment (2002-2003) and followed for a mean of 9.7 years (SD=3.83).

The e-DII was calculated based on a food frequency questionnaire (FFQ) at baseline and categorized into quartiles with lower e-DII scores representing a more anti-inflammatory diet. Incident PrCA cases were ascertained via linkage with the Kaiser Permanente Northern California Cancer Registry (KPNCCR) and were categorized into three groups: high-risk intermediate-high and low-risk. Accelerated failure time models with log-logistic distribution were fit to model time-to-development of incident PrCA. Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) of high- and intermediate- risk PrCA. In all analyses, the lowest quartile of e-DII was used as the referent group.

Results: Time-to-development of incident total PrCA did not differ by quartile of e-DII, although there was a suggestion of a shorter time to diagnosis for those in the highest quartile (Acceleration Factor $(AF)_{Q4\ vs.Q1}$=1.07; 95%CI:0.95-1.20). In race-stratified analyses, the time to diagnosis was significantly shortened only among Whites ($AF_{Q4\ vs.Q1}$=1.16; 95%CI:1.01-1.34). The HR for high-risk PrCA was increased by 36% in the third quartile of the e-DII ($HR_{Q3\ vs.Q1}$=1.36; 95%CI:1.04-1.76); however, there was no

increased risk in the fourth quartile ($HR_{Q4\ vs.Q1}$=0.99; 95%CI:0.74-1.32, p_{trend}=0.74). The HR for high-risk PrCA was the highest among Blacks ($HR_{Q3\ vs.Q1}$=3.77; 95%CI:1.29-11.06) and Other ($HR_{continuous}$=1.23; 95%CI:1.03-1.48). The e-DII was not associated with intermediate- and low-risk PrCA incidence.

Conclusions: Pro-inflammatory diet may contribute to increased risk of high-risk PrCA, especially, among Blacks.

Introduction

In the United States, prostate cancer (PrCA) is the most frequently diagnosed and the second most common cause of cancer death among men (72, 73). During the last 15 years, PrCA mortality rates in the US decreased from 38.6 to 24.6 per 100,000, most likely due to widespread population-based screening and improved treatment. Despite this, the absolute number of incident PrCA is expected to increase substantially as baby-boomers age (260). In the United States, PrCA incidence and mortality rates vary by race and are the highest among African Americans who tend to be diagnosed at a younger age and with more aggressive disease than their European-American counterparts (72, 73). According to age-adjusted estimates for 2013, PrCA incidence in African Americans is 70% and mortality is 2.4 times higher than in European Americans (72, 73). PrCA incidence and mortality in Hispanics/Latino and Asian-Americans are lower than in African- and European Americans (73).

Few modifiable PrCA risk factors have been established. Thus, further characterization of PrCA risk factors is important for bolstering prevention efforts.

Currently, only increasing age, African ancestry, and a family history of the PrCA are considered well-established PrCA risk factors (73). Evidence suggests that persistent inflammation within the prostate due to infections, physical trauma, urine reflux, hormonal changes, diabetes, dietary exposures or other environmental factors may play a role in development of PrCA (136, 138, 261). Increased levels of the inflammatory markers, C-reactive protein (CRP) in circulation and transcripts of interleukin (IL)-6 gene in prostate tissue, have been observed among men with PrCA compared to those with benign prostatic hyperplasia (262, 263). A biological pathway of innate immunity and inflammation has been associated with risk of advanced PrCA (264). There is evidence that diet may influence PrCA risk via modulation of inflammation. For instance, heterocyclic amines, strong dietary mutagens produced in high quantities when cooking meat, have been associated with prostatic inflammation in animal models, and with increased PrCA risk in epidemiologic studies (261, 265, 266). In contrast, phytochemicals contained in cruciferous vegetables (e.g., kale, cauliflower and Brussels sprouts) exert anti-oxidant, pro-apoptotic, anti-proliferative and anti-metastatic effects in PrCA cells *in vitro,* and in animal models (158). It has been reported that some racial/ethnic minorities are more likely to have diets with low fruit and vegetable consumption and sedentary lifestyles as compared to non-Hispanic Whites (149-151). Such lifestyle patterns have been associated with high levels of systemic inflammation, as expressed by increased levels of CRP (149-151).

Few epidemiologic studies have investigated interrelationships between diet, inflammation and PrCA (82, 181, 267). Investigators at the University of South Carolina's Cancer Prevention and Control Program, created the Dietary Inflammatory

Index (DII)^{TM}, which calculates the overall inflammatory potential of an individual's diet (81). The major advantage of the DII over other dietary indices is that it measures the inflammatory potential of the individual's diet based on reported intakes. DII calculation is based on previous research that entailed reading and scoring nearly 2,000 articles focusing specifically on inflammation (160). Additionally, individuals' DII scores are standardized against a range of actual food intakes observed in 11 different populations around the world, which facilitates comparability between populations (160). In previous studies, the DII predicted increased levels of several inflammatory biomarkers including: CRP (83, 177), IL-6 (169, 170, 179), tumor necrosis factor alpha (170) and homocysteine (169). A higher, pro-inflammatory DII has been associated with increased risk of colorectal (174, 180, 268-270), pancreatic (176), and esophageal (165, 271) cancer, asthma (179), and cardiovascular disease (272).

To date, three investigations examined the relationship between the DII and PrCA risk; two case-control (82, 181) and one prospective study (267). Men in the highest (most pro-inflammatory) quartile of the DII had significantly higher risk of PrCA than those in the first quartile.

The current study characterized the relationship between dietary inflammation potential and PrCA risk in a prospective cohort study of California men of varying racial and ethnic composition. The hypotheses of this study was that men with higher (i.e., pro-inflammatory) DII scores had elevated PrCA risk and a higher risk of more aggressive PrCA relative to those with anti-inflammatory diets. It was further hypothesized that these associations would be stronger among African Americans compared with other races.

Methods

Study population

The California Men's Health Study (CMHS) is a large multiethnic cohort of U.S. male members of Kaiser Permanente (KP), a health insurance provider that covers a large number of residents of Northern and Southern California. In 2002-2003 the CMHS recruited 84,170 men 45-69 years of age; 40% of whom were from minority populations, including Chinese, Hispanic and African Americans. Information about the CMHS recruitment and data collection procedures are described in detail elsewhere (206). Briefly, comprehensive information on participants' demographics, health status, family history of PrCA, medication and supplementation use, and potential PrCA risk factors such as diet, physical activity and sleep were collected upon enrollment via two mailed questionnaires (206). All participants provided informed consent and this study was approved by the Institutional Review boards of Kaiser Permanente Northern California and the University of Southern Carolina.

The study population was comprised of CMHS participants (Northern California region only) who had active KP membership for at least one year prior to the enrollment into the CMHS. Individuals were excluded if they: had any cancer except non-melanoma skin cancer (n=1,363) at enrollment, were missing information on race/ethnicity (n=346), or had implausible total daily energy intake (<500 kcal or >6000 kcal, n=958). Participants who developed PrCA during follow-up but were missing information on PrCA stage (SEER) also were excluded (n=65).

PrCA ascertainment

The ascertainment of incident PrCA cases was performed via linkage of CMHS members to the Kaiser Permanente Northern California Cancer Registry. California state law requires reporting of all incident cancer cases, and the KPNCCR ascertains and reports all cases according to the standards established by the National Cancer Institute's Surveillance, Epidemiology, and End Result Program (SEER).

In this study, PrCA was categorized into three groups using the updated (2010) version of the standard PrCA staging system endorsed by the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) (212). The high-risk PrCA group included men with clinically localized high-risk PrCA and advanced, very high-risk PrCA (≥T3a or PSA>20 ng/ml, or a Gleason score of 8-10, or those who died from PrCA). The clinically localized, intermediate-risk group consisted of men with T2b-T2c, or T1-T2a and PSA10-20, or T1-T2a and a Gleason score of 7. All other men with PrCA were in the clinically localized, low-risk PrCA group.

Dietary assessment

Information about usual diet during the previous year was obtained at baseline from a self-administered semi-quantitative food frequency questionnaire (FFQ) using a version of the Women's Health Initiative FFQ that was modified for use in men and validated in several studies (207-209). The nutrient contents of an individual's diet were calculated using the Nutrition Data Systems for Research software (NDSR) (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA). The FFQ

provided information on 27 individual food parameters needed to compute DII scores (carbohydrate, protein, total fat, alcohol, fiber, cholesterol, saturated fat, MUFA, PUFA, omega-3, omega-6, trans-fat, Niacin, Thiamin, Riboflavin, B12, B6, Iron, Magnesium, Zinc, Selenium, vitamin-A, vitamin-C, vitamin-D, vitamin-E, folic acid, and beta carotene). An individual DII score was computed for each study participant who completed the FFQ, as described previously (80, 81).

Briefly, for each food parameter in the DII calculation, its "global" mean and standard deviation were obtained using a "world" database compiled from 11 countries around the world (USA, Mexico, England, Denmark, India, Australia, New Zealand, Bahrain, Scotland, South Korea and Japan) (82). For each participant, this global mean was then subtracted from the amount of consumed nutrient and divided by the global standard deviation, yielding a food-specific z-score. The z-scores were then converted into percentile scores in order to minimize the effect of the right skew characteristic of dietary data. In order to center the values around zero, these values were doubled and 1 was subtracted from each value. These centered percentile scores were multiplied by an inflammatory effect score previously derived for each food parameter based on an extensive literature review and evidence ranking of 1,943 relevant peer-reviewed publications (80, 81). The percentile-scores for all food parameters were summed to produce a DII score for each study participant which was further adjusted for energy (e-DII). Intakes for the 27 food parameters were divided by total estimated energy intake and multiplied by 1,000. The same technique was applied to the world standard database. More negative e-DII scores are associated with anti-inflammatory potential, whereas more positive scores are indicative of more pro-inflammatory potential (160).

Confounder assessment

Information on all potential confounders was collected at baseline via questionnaire and medical record review. Physical activity was assessed using questions adopted from the Coronary Artery Risk Development in Young Adults (CARDIA) Physical Activity History (210). Analysis of frequency, duration and intensity of recreational, household and occupational activities yielded a total physical activity estimate in MET-hours per week (206). The following variables were tested as potential confounders for inclusion in statistical models: race (White, Black, Asian, Hispanic, Other), age at baseline (5-year intervals for the overall PrCA risk estimates and 45-55, 56-65, 65-70 years for subgroup analyses), body mass index (BMI) calculated from self-reported weight in kilograms divided by square height in meters (< 25, 25-29.9, ≥30 kg/m^2), education (high school equivalent or less; vocational or technical school; some college, associate or bachelor degree; graduate/professional school), smoking status (current or former smokers vs. non-smoker), income (<$40,000, $40,000-$59,000, $60-$80,000, $80-100,000, >$100,000), regular use of non-steroidal anti inflammatory medicines (NSAID) (Yes/No), regular multivitamin use (Yes/No), sleep duration (≤6, 7, ≥8 hrs), total physical activity (0-359, 360-1102, 1103-2201, > 2202 MET-min/week), history of diabetes of any type (Yes/No; recorded diagnosis in the Northern California KP Diabetes Registry), family history of PrCA in a first-degree relative (Yes/No), and benign prostatic hyperplasia (BPH).

Statistical analysis

The follow-up time was censored at: diagnosis of incident PrCA, death, gap in KP membership exceeding 90 days, or the end of the study (December 31, 2014), whichever

came first. The e-DII was categorized into quartiles based on the distribution in all participants in the analytic sample (Q1: -6.19 to -3.36; -3.37 to -2.03; -2.04 to -0.55; -0.56 to 4.89). To address potential confounding, variables with >10% missing values were recoded using indicator variables which had missing values as a separate category. A manual backwards selection procedure was used to identify covariates for inclusion in multivariable models. Variables were retained in the final statistical models if their exclusion resulted in a change in the effect estimate for e-DII by ≥10%. Statistically significant covariates ($\alpha<0.05$) also were retained in the final statistical models. The proportional hazards assumption was tested using graphical (Kaplan-Meyer survival plots) and regression approaches (cumulative Martingale residuals). Effect modification was tested using two approaches: Likelihood Ratio Test (LRT) for significance of the interaction term added to the final model, and stratification of the analysis based on differing levels of the effect modifier.

In the analysis of the relationships between e-DII and the risk of total PrCA (PrCA of any stage), the proportional hazards assumption for the e-DII (quartiles) was not met; thus, the parametric accelerated failure time model was used with a log-logistic distribution (273). Since the proportional odds assumption was not met, only the acceleration factor, with 95% confidence interval (CI) was presented.

Cox proportional hazards models were used to assess the relationships between the e-DII and either high- or intermediate-risk PrCA. The proportional hazards assumption was violated for sleep and age; therefore, these variables were placed in the STRATA statement in the PHREG procedure in SAS®. For linear trend tests, the median

of each e-DII quartile was included in statistical models as a continuous variable with adjustment for the same confounders that were included in the previous analyses.

Sensitivity analyses were conducted to explore the possible effects of missing data on the results. Men diagnosed with PrCA during the first 3 years of follow-up were excluded in order to assess the possibility of reverse causality. In separate analyses, all participants with missing sleep duration were excluded, and analyses were then repeated after removal of the sleep duration variable from the statistical models.

All statistical analyses were performed using SAS® 9.4 (Cary, North Carolina) with significance levels set at $\alpha=0.05$.

Results

The analytical sample consisted from 40,161 men with mean follow-up of 9.7 years (SD=3.83). From 2002-2003 until December 31, 2014, a total of 2,707 CMHS participants were diagnosed with incident PrCA.

Participants' characteristics at baseline by quartile of e-DII are presented in Table 6.1. Men in lower quartiles of e-DII were older than those in the upper quartiles. The proportion of Whites slightly decreased across quartiles of e-DII, while proportion of Blacks and Hispanics increased. Compared to the first (anti-inflammatory) quartile of e-DII, men in the fourth (pro-inflammatory) quartile were more obese, and had lower educational attainment and income. The proportion of single men increased with quartile of e-DII, as physical activity and sleep duration decreased. The proportion of smokers

and regular nonsteroidal anti-inflammatory drug (NSAID) users increased with quartiles of e-DII, while the proportion of regular multivitamin users decreased.

There was no statistically significant difference in time to development of incident total PrCA between quartiles of e-DII after adjustment for the effects of age, race, BPH, family history of PrCA, diabetes, and smoking status (Table 2). Men in the highest quartile of e-DII developed incident PrCA 7% faster than those in the lowest quartile (acceleration factor (AF)=1.07; 95%CI: 0.95-1.20). Exclusion of men who were diagnosed during the first 3 years of follow-up did not alter the relationship between quartiles of e-DII and incident PrCA (Table 2). In separate sensitivity analyses, exclusion of those with missing sleep duration, or adjustment for this variable, did not change the results (Table 6.2). Race modified the relationship between the e-DII and overall PrCA risk (LRT p=0.0001). In the race-stratified analyses, White men in the fourth quartile of e-DII had a shorter time (16%) to PrCA diagnosis (AF=1.16;95%CI:1.01-1.34). Among Black men in the third quartile of e-DII, the time to development of PrCA was longer (35%) (AR=0.65; 95%CI:0.44-0.96).

Compared to the first quartile of e-DII, HRs for high-risk PrCA increased by 27% and 36%, respectively, in the second and third quartiles (hazard ratio $(HR)_{Q2vs.Q1}$=1.27; 95%CI:0.98-1.66, and $HR_{Q3\ vs.\ Q1}$ =1.36; 95%CI: 1.04-1.76), although there was no association between the highest and the lowest e-DII quartiles (HR=0.99;95%CI:0.74-1.32) (Table 6.3). Relationships between e-DII and high-risk PrCA were modified by race (LRT p=0.0002). In race-stratified analyses, high-risk PrCA among Blacks increased across e-DII quartiles and was elevated by nearly four-fold among those in the third e-DII quartile ($HR_{Q3\ vs.\ Q1}$=3.77; 95%CI:1.29-11.06). Among participants in the multi-

ethnic/other category, there was a 23% increase in high-risk PrCA per unit e-DII (HR=1.23;95%:1.03-1.48, Table 6.3). No relationship was observed between e-DII and the risk of intermediate-risk PrCA (Table 6.3) or low-risk PrCA (data not shown).

Discussion

In this study, the e-DII was not significantly associated with time-to-development of PrCA when all cases were considered simultaneously. Estimates of the acceleration factor suggested that it took slightly less time (7%) for men in the most pro-inflammatory quartile of e-DII to develop incident PrCA compared to those in the lowest e-DII quartile, but the effect was not statistically significant. Assessment of potential reverse causality via exclusion of men who developed PrCA during the first 3 years of follow-up did not change the results. However, a statistically significant 16% decrease in time to total PrCA development was found among White men with the most pro-inflammatory diets. When only high-risk PrCA was examined, there was an increased risk with increasing e-DII, although it was the highest in the third rather than the fourth quartile. Thus, interpretation of the results is complicated by an apparent lack of monotonic dose-response across quartiles of e-DII, and by a lack of association when using e-DII as a continuous variable. Furthermore, the inflammatory potential of the diet was not associated with intermediate-risk PrCA.

To date, three studies have examined the relationship between DII scores and PrCA. Two case-control studies explored these relationships among Italian and Jamaican men (82, 181). In the Jamaican study, 229 incident PrCA cases and 250 PrCA-free controls were recruited from the same urology clinics, two large hospitals and private

practices between 2006 and 2007 (181). Jamaican men in the highest quartile of the DII had 2.4 times increased risk of total PrCA relative to men in the "healthiest" first quartile. Consistent with that result, a prospective study in France found that men in the highest quartile of the DII had PrCA risks 2.1 times higher than those with anti-inflammatory diets (267). Of note, the test for PrCA trend across quartiles of DII was not statistically significant. In a large case-control study conducted in Southern Italy, PrCA risk among men in the fourth DII quartile was 33% higher than in those in the first quartile (82). In the current study, no statistically significant differences in time to development of total PrCA were detected between the lowest and the highest quartiles of e-DII. However, in a race-stratified analyses, White men in the highest quartile of e-DII had a shorter time (by 16%) to development of PrCA, which is closer to the risk estimates reported for the above-mentioned case-control study among Italian men (82).

The lack of statistically significant association between e-DII and total PrCA prior to stratification by race may be attributed to several factors. It is plausible that the relationship between dietary inflammation potential and PrCA risk may vary by disease aggressiveness and race. In the Jamaican study, more than 50% of PrCA cases were high-grade (Gleason score ≥7), and all participants were of African descent (181, 274). In this study, the high-risk PrCA cases represented only 18% of the total number of cases and Black men represented only 6% of the study population. In race-stratified analyses, the relationship between e-DII and high-risk PrCA was the strongest and statistically significant only among Blacks and those in the Multiethnic/Other group (this latter group included men of races/ethnicities other than Black or White, and could have included those of mixed race with some African admixture). The risk estimates for e-DII and high-

risk PrCA among Blacks were similar in magnitude to overall PrCA risk in the Jamaican study (181). Also, DII scores in this study were generally lower than what we see in most studies examining the role of DII in health.

It is not clear why increased incidence of high-risk PrCA was observed in the third, but not in the highest (i.e., most pro-inflammatory), quartile of the e-DII. In ancillary analyses, change of cut-off points (e.g. tertiles or quintiles) did not meaningfully alter the results. In secondary analyses with DII and total energy intake as a separate variable, the risk of high-risk PrCA did not differ between second, third and forth quartiles of DII (HR=1.11;95%CI:0.76-1.63). After exclusion of cases diagnosed during first 3 years of follow up, the risk of high-risk PrCA was the highest in fourth quartile but was not statistically significant (HR=1.25;95%CI:0.81-1.91).

In the study among Italian men, the risk of total PrCA in the fourth quartile of e-DII was practically the same as in the third quartile ($OR_{Quartile4v.1}$ =1.33, 95% CI: 1.01-1.76 vs. $OR_{Quartile3v.1}$=1.32, 95% CI:1.03-1.69, respectively) and there was no statistically significant trend in the other two studies (181, 267). These observations may suggest the possibility of a non-linear relationship between diet and PrCA, and a possible threshold effect. The study among French men investigated dose-response relationships between the DII and prostate cancer using restricted cubic splines (267). Men with DII ≥ -1.0 had 2.3-fold increased PrCA risk relative to those with DII < -1.0 (HR: 2.31; 95%CI: 1.35-3.95; P =0.002) (267). Previously, increased PrCA risk among men in the Jamaican, Italian and French studies were observed for DII quartiles that were ≥ -1.0 (82, 181, 267). In this study, the incidence of high-risk PrCA was significantly increased only in the third quartile that included e-DII values of ≥ -1.0 (Q_3: -2.0313 to ≤ -0.5517). The absence of

increased PrCA risk among those in the highest e-DII quartile also may be related to confounding by unknown factor, measurement error, or may suggest an overall lack of association.

Differences in dietary intakes and food parameters available for the DII calculations and use of the e-DII instead of the DII to calculate risk, have contributed to the differences in the risk estimates between this study and others published to date. For instance, the first and second quartiles of e-DII in this study were considerably more negative than those in the previous PrCA studies (82, 181, 267). The range of actual DII in this study was clearly larger (-6.28 to 4.69) than in other PrCA studies: Jamaican study (-3.14 to 2.77) and the French study (-5.0 to 5.3) (82, 181, 267). Compared to other large cohorts, such as National Institutes of Health–American Associations of Retired Persons Diet and Health Study individuals (NIH-AARP), that explored the relationships between the DII and a risk of colorectal cancer, quartiles in this study were more negative, indicating an overall healthier diet in this study population (174).

The strengths of this study include a robust sample size among a diverse cohort with prospectively collected data, extended follow-up (up to 12 years), rigorous case ascertainment, and ample information on potential confounders. Because the diet was assessed prior to the development of the outcome, differential recall was not an issue. The sensitivity analyses indicated that, after the exclusion of cases diagnosed during the first 3 years of follow-up, the results did not change; thus, it is unlikely that reverse causation played a significant role. About forty percent of the study population was represented by different racial and ethnic groups (Asian, Black, Hispanic and Filipinos). The FFQ was modified for use among men and to include foods commonly eaten by previously

mentioned ethnic groups; it was also translated into Spanish and Chinese. Thus, any significant misclassification of the exposure is unlikely.

One limitation of this study is that the information about diet was assessed only at baseline with a single FFQ. Thus, it is possible that temporal changes in inflammatory effect of diet on tumor development could not be captured. Previous research indicates that dietary patterns in adulthood are fairly stable over time (275-278). Moreover, previous large prospective studies that used diet assessment only at baseline found that higher DII scores were associated with statistically significant increased risks for chronic disease, including cancer, and increased mortality (171, 174, 175, 270).

Another study limitation was that the sample sizes and statistical power may have been limited for assessment of the relationship between the e-DII and PrCA risk among sub-strata of race or PrCA aggressiveness.

In summary, the results of this study suggest that a pro-inflammatory diet was associated with 16% increase in total PrCA risk among middle-age White men. The inflammatory potential of diet was associated with increases in high-risk PrCA incidence. However, the patterns of risk observed across quartiles complicate the interpretation, suggesting either a complex dose-response pattern (non-linear relationship with possible threshold effect), or a lack of association. The relationship between the inflammatory potential of a diet and PrCA may vary by race; Blacks and those of non-White (or mixed) races may be more susceptible. The relationship between dietary inflammatory potential and risk of advanced /aggressive disease merits further investigation, particularly among those of racial or ethnic minorities.

Table 6.1 Participants' characteristics (n, %) by quartiles of Energy-Density Dietary Inflammatory Index at baseline, California Men's Health Study 2002-2014				
Characteristic	**Q1: -6.1940 to ≤-3.3597 (the healthiest) n= 10042**	**Q2: -3.3597 to ≤-2.0313 n= 10040**	**Q3: -2.0313 to ≤-0.5517 n= 10040**	**Q4: -0.5517 to 4.8927 (the least healthy) n=10039**
Age at baseline				
44-50	1649 (16.4)	1884 (18.8)	2122 (21.1)	2447 (24.4)
51-55	2006 (20.0)	2173 (21.6)	2236 (22.3)	2363 (24.5)
56-60	2223 (22.1)	2132 (21.2)	2126 (21.2)	2136 (21.3)
61- 65	2312 (23.1)	2050 (20.4)	1936 (19.3)	1731 (17.2)
66-70	1852 (18.4)	1801 (18.0)	1620 (16.1)	1362 (13.6)
Race				
White	6989 (69.6)	6555 (65.3)	6380 (63.6)	6212 (61.9)
Black	429 (4.3)	483 (4.8)	606 (6.0)	801 (8.0)
Asian	973 (9.7)	1128 (11.2)	923 (9.2)	852 (8.5)
Hispanic	793 (7.9)	973 (9.7)	1148 (11.4)	1121 (11.2)
Multiethnic/Other	858 (8.5)	901 (9.0)	983 (9.8)	1053 (10.5)
Body mass index , kg/m^2				
Normal, < 25	3388 (33.7)	2876 (28.7)	2488 (24.8)	2191 (21.8)
Overweight, 25 to <30	4572 (45.5)	4694 (46.7)	4750 (47.3)	4442 (44.3)
Obese, ≥30	1946 (19.4)	2329 (23.2)	2660 (26.5)	3210 (32.0)
Education				
High school, equivalent or less	1510 (15.0)	1934 (12.3)	2349 (23.4)	2822 (28.1)
Vocational/tech school	2451 (24.4)	2766 (27.6)	2977 (29.7)	3393 (33.8)
Some college, associate or bachelor degree	2267 (22.6)	2304 (22.9)	2304 (22.9)	2019 (20.1)
Graduate/professional school	3776 (37.6)	2996 (29.8)	2377 (23.7)	1753 (14.5)
Missing	38 (0.4)	40 (0.4)	33 (0.3)	52 (0.5)
Income, $				
<40,000	1421 (14.1)	1630 (16.2)	1850 (18.4)	2112 (21.0)
40-59,000	1565 (15.6)	1772 (17.7)	1864 (18.6)	2020 (20.1)
60-80,000	1649 (16.4)	1784 (17.8)	1861 (18.5)	1865 (18.6)
80-100,000	1382 (13.8)	1433 (14.3)	1352 (13.5)	1370 (13.7)
>100,000	3616 (36.0)	3026 (30.1)	2745 (27.3)	2296 (22.9)
Missing	409 (4.1)	395 (3.9)	368 (3.7)	376 (3.7)
Marital status				
Married/living with a partner	8463 (84.3)	8322 (82.9)	8234 (82.0)	7871 (78.4)
Single	1539 (15.3)	1699 (16.9)	1776 (17.7)	2129 (21.2)
Missing	40 (0.4)	19 (0.2)	30 (0.3)	39 (0.4)
Total physical activity, MET-min/week				

0-359	1401 (13.9)	2125 (21.2)	2744 (27.3)	3749 (37.3)
360-1102	2229 (22.2)	2504 (24.9)	2649 (26.4)	2635 (26.2)
1103-2201	2743 (27.3)	2638 (26.3)	2488 (24.8)	2144 (21.4)
>2202	3653 (36.4)	2753 (27.4)	2137 (21.3)	1484 (14.8)
Missing	16 (0.2)	20 (0.2)	22 (0.2)	27 (0.3)
Sleep duration, hr/day				
≤6	2115 (21.1)	2209 (22.0)	2235 (22.3)	2271 (22.6)
7	2959 (29.5)	2733 (27.2)	2574 (25.6)	2278 (22.7)
≥8	2284 (22.7)	2085 (20.8)	2055 (20.5)	1873 (18.7)
Missing	2684 (26.7)	3013 (30.0)	3176 (31.6)	3617 (36.3)
NSAID regular[1] use				
No	7032 (70.0)	6851 (68.2)	6646 (66.2)	6556 (65.3)
Yes	1268 (12.6)	1330 (13.3)	1478 (14.7)	1607 (16.0)
Missing	1742 (17.4)	1859 (18.5)	1916 (19.1)	1876 (18.7)
Multivitamin regular[1] use				
No	4392 (43.7)	5022 (50.0)	5430 (54.1)	6034 (60.1)
Yes	5650 (56.3)	5018 (50.0)	4610 (45.9)	4005 (39.9)
Smoking status				
Non-smoker	4626 (46.1)	4471 (44.5)	4150 (41.3)	3692 (36.8)
Former smoker	4666 (46.5)	4544 (45.3)	4601 (45.8)	4430 (44.1)
Current smoker	511 (5.1)	782 (7.8)	1061 (10.6)	1624 (16.2)
Missing	239 (2.4)	243 (2.4)	228 (2.3)	293 (2.9)
Diabetes				
No	8894 (88.6)	8805 (87.7)	8753 (87.2)	8883 (88.5)
Yes	1148 (11.4)	1235 (12.3)	1287 (12.8)	1156 (11.5)
Benign prostatic hyperplasia				
No	7459 (74.3)	7548 (75.2)	7691 (76.6)	7899 (78.7)
Yes	2201 (21.9)	2075 (20.7)	1897 (18.9)	1705 (17.0)
Missing	382 (3.8)	417 (4.2)	452 (4.5)	435 (4.3)
Family history of prostate cancer[2]				
No	8792 (87.6)	8811 (87.8)	8737 (87.0)	8799 (87.6)
Yes	1250 (12.4)	1229 (12.2)	1303 (13.0)	1240 (12.4)

[1] Use 3-4 times per week.
[2] Father or brother had prostate cancer.

Table 6.2 Relationships between quartiles of Energy-Density DII and incidence of Prostate Cancer of any stage						
		Q1: -6.1940 to ≤-3.3597	**Q2:- 3.3598 to ≤-2.0313**	**Q3: -2.0314 to ≤-0.5517**	**Q4: -0.5518 to 4.8927**	**e-DII continuous, AF (95%CI)**
Sleep duration is not included in confounder selection	N with PrCA	640	621	621	522	2,404
	AF (95%CI)[1]	1.00 (Ref.)	0.98 (0.88-1.09)	0.95 (0.85-1.06)	1.05 (0.94-1.18)	1.01 (0.98-1.03)
Sleep duration modeled as a dummy variable	N with PrCA	636	609	616	514	2,375
	AF (95%CI)[2]	1.00 (Ref.)	0.998 (0.90-1.11)	0.96 (0.86-1.06)	1.07 (0.95-1.20)	1.01 (0.99-1.03)
Men with missing sleep duration removed	N with PrCA[2]	461	428	449	345	1,683
	AF (95%CI)[2]	1.00 (Ref.)	0.995 (0.90-1.11)	0.92 (0.83-1.02)	1.04 (0.93-1.16)	1.00 (0.98-1.02)
Men diagnosed with prostate cancer during first 3 y. of follow up removed	N with PrCA[2]	456	441	483	372	1,752
	AF (95%CI)[2]	1.00 (Ref.)	0.99 (0.92-1.07)	0.92 (0.85-0.99)	1.03 (0.95-1.11)	1.00 (0.98-1.01)
Stratified by Race						
White	N with PrCA	481	423	418	315	1,637
	AF (95%CI)[2]	1.00 (Ref.)	1.02 (0.90-1.16)	0.96 (0.84-1.09)	1.16 (1.01-1.34)	1.02 (1.00-1.05)
Black	N with PrCA	35	44	73	74	226
	AF (95%CI)[2]	1.00 (Ref.)	0.89 (0.58-1.36)	0.65 (0.44-0.96)	0.75 (0.50-1.11)	0.95 (0.89-1.02)
Asian	N with PrCA	41	52	38	30	161
	AF (95%CI)[2]	1.00 (Ref.)	0.92 (0.60-1.40)	0.95 (0.60-1.51)	0.99 (0.61-1.62)	1.03 (0.94-1.14)
Hispanic	N with PrCA	45	48	45	45	183
	AF (95%CI)[2]	1.00 (Ref.)	1.09 (0.75-1.59)	1.36 (0.93-1.99)	1.22 (0.83-1.80)	1.04 (0.97-1.13)
Multiethnic/Other	N with PrCA	34	42	42	50	168
	AF (95%CI)[2]	1.00 (Ref.)	0.79 (0.51-1.22)	0.80 (0.52-1.23)	0.68 (0.44-1.04)	0.92 (0.85-1.00)

Detailed legend: Accelerated failure time models with log-logistic distribution were used to estimate parameters.
AF: acceleration factor, CI: confidence interval, PrCA: Prostate Cancer.
[1] Adjusted for age (in 5-year intervals), race, BPH, prostate cancer family history, diabetes, and smoking status. Only significant confounders were kept in the model.
[2] Adjusted for age (in 5-year intervals), race, sleep (categorical), BPH, BMI (categorical), prostate cancer family history, diabetes, and smoking status. Physical activity was not a significant confounder.

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Table 6.3 Relationships between Energy-Density DII and High- and Intermediate-high risk Prostate Cancer						
	Q1: -6.1940 to ≤-3.3597 (healthiest)	**Q2:- 3.3598 to ≤-2.0313**	**Q3: -2.0314 to ≤-0.5517**	**Q4: -0.5518 to ≤4.8927 (least healthy)**	**p-value for tend**	**e-DII continuous, HR (95%CI)**
High-risk prostate cancer						
N with prostate cancer	100	123	126	88		437
Age adjusted, HR (95%CI)	1.00 (Ref.)	1.28 (0.98-1.67)	1.39 (1.07-1.80)	1.04 (0.78-1.38)	0.97	1.03 (0.98-1.08)
HR (95%CI)[1]	1.00 (Ref.)	1.27 (0.98-1.66)	1.36 (1.04-1.76)	0.99 (0.74-1.32)	0.74	1.02 (0.96-1.07)
Men with missing sleep duration excluded						
N with prostate cancer	78	87	99	57		321
HR (95%CI)[1]	1.00 (Ref.)	1.19 (0.88-1.62)	1.44 (1.07-1.94)	0.91 (0.65-1.28)	0.91	1.02 (0.96-1.08)
Cases diagnosed during first 3 years removed						
N with prostate cancer	83	94	103	67		347
HR (95%CI)[1]	1.00 (Ref.)	1.19 (0.88-1.59)	1.35 (1.01-1.81)	0.93 (0.67-1.28)	0.99	1.02 (0.96-1.08)
Stratified by race[1]						
White with prostate cancer (n)	73	86	69	46		274
HR (95%CI)[1]	1.00 (Ref.)	1.29 (0.95-1.76)	1.12 (0.81-1.56)	0.80 (0.55-1.16)	NA	0.97 (0.91-1.04)
Black with prostate cancer (n)	4	11	20	15		50
HR (95%CI)[1]	1.00 (Ref.)	2.43 (0.77-7.64)	3.77 (1.29-11.06)	2.29 (0.76-6.94)	NA	1.10 (0.95-1.28)
Asian with prostate cancer (n)	10	11	13	6		40
HR (95%CI)[1]	1.00 (Ref.)	0.97 (0.41-2.30)	1.51 (0.66-3.46)	0.81 (0.30-2.24)	NA	1.03 (0.87-1.24)
Hispanic with prostate cancer (n)	9	9	13	11		42
HR (95%CI)[1]	1.00 (Ref.)	0.91 (0.36-2.28)	1.16 (0.49-2.72)	1.11 (0.46-2.70)	NA	1.04 (0.88-1.23)
Multiethnic/Other with prostate cancer (n)	4	6	9	11		30
HR (95%CI)[1]	1.00 (Ref.)	1.68 (0.47-5.97)	2.97 (0.94-9.34)	2.94 (0.92-9.43)	NA	1.23 (1.03-1.48)
Intermediate-risk prostate cancer						
N with prostate cancer	237	242	239	201		919
Age adjusted, HR (95%CI)	1.00 (Ref.)	1.06 (0.88-1.26)	1.08 (0.90-1.30)	0.96 (0.79-1.16)	0.70	0.99 (0.96-1.03)
HR (95%CI)[2]	1.00 (Ref.)	1.05 (0.88-1.26)	1.06 (0.88-1.26)	0.91 (0.76-1.10)	0.36	0.98 (0.95-1.02)

Men with missing sleep duration excluded						
N with prostate cancer	172	168	185	131		656
HR (95%CI)[2]	1.00 (Ref.)	1.05 (0.85-1.30)	1.20 (0.98-1.48)	0.93 (0.74-1.17)	0.84	1.00 (0.96-1.04)
Cases diagnosed during first 3 years removed						
N with prostate cancer	180	174	195	144		693
HR (95%CI)[2]	1.00 (Ref.)	1.01 (0.82-1.24)	1.15 (0.94-1.41)	0.89 (0.71-1.11)	0.53	0.99 (0.95-1.03)

Detailed legend: Cox proportional hazards models were used to calculate parameters.
[1]Adjusted for race and BPH; sleep duration (categorical) and age (≤55, 55-65, >65 y.) are in strata statement. Physical activity was not a significant confounder.
[2] Adjusted for race, BPH, family history of prostate cancer; sleep duration (categorical) and age (≤55, 55-65, >65 y.) are in strata statement.

CHAPTER 7

Summary

This study showed that disrupted sleep and social jetlag in adults 21-35 years of age remained stable within two years. By the end of the study, chronotype became on average, 23 minutes earlier, most likely due to the phase advance among participants with evening chronotypes. Whether the observations in the present study correspond to more chronic sleep disruption that extends beyond two years remains to be determined. The demographic characteristics identified in this study that may contribute to persistent sleep disruption include: male sex, being a student, non-White race, low income, and evening chronotype. The further identification of susceptible subgroups of young adults with persistent sleep disruption may provide a health benefit to those individuals in terms of chronic disease prevention, given the persistent character of insomnia and other sleep disorders and their reported association with chronic diseases such as depression (37, 220, 239), obesity (213, 240, 241), diabetes (62, 120), hypertension (63, 118, 242), CVD (65) and cancer (28).

Chronotype and SJL were not associated with any anthropometric indexes of metabolic disorder. The relationships between disrupted sleep (SOL, SE, TST) and central obesity or elevated SBP were only modest. Despite being a fairly strong predictor for all sleep measures except SOL, chronotype seemed to modify rather than confound the relationships between disrupted sleep and obesity or high blood pressure. Those with poor sleep and morning chronotype were more likely to have excess body fat and central

obesity. Evening types seemed to be more resilient to detrimental effects of sleep disruption than morning types and only had increased chance of having high SBP if they slept <6 hours. The discovery of the effect-modifying role of chronotype is novel compared to the previous studies that either inferred that chronotype, SJL and sleep confound each other's relationships with metabolic disorder (12, 49, 58) or that SJL mediates the relationships between chronotype and obesity (56). Due to the lack of association between chronotype or SJL with anthropometric measures, we were unable totest the latter hypothesis. This study's findings suggest that the relationships between sleep, chronotype, SJL and anthropometric indices are more complex than it was previously hypothesized and deserve further investigation in the future studies.

A pro-inflammatory diet was associated with 16% increase in total PrCA risk among middle-age White men while among all race combined the results were only suggestive. The inflammatory potential of diet was associated with increases in high-risk PrCA incidence. However, the patterns of risk observed across quartiles of e-DII complicate the interpretation, suggesting either a complex dose-response pattern (non-linear relationship with possible threshold effect), or a lack of association. The relationship between the inflammatory potential of a diet and PrCA may vary by race; Blacks and those of non-White (or mixed) races may be more susceptible. The relationship between dietary inflammatory potential and risk of advanced /aggressive disease merits further investigation, particularly among those of racial or ethnic minorities.

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APPENDIX A

Chronotype estimation

Time (in minutes) from midnight to the sleep onset the next day and from the following midnight to the wake up time on the following day was calculated using the SWA data. During calculation of chronotype, minutes were converted into hours. Since the information on work schedule was not collected in this study, it was assumed that free days occurred only on weekends. The first step in calculation of chronotype was calculation of the mid-point of sleep on free days (MSF) using the following formulas:

a. If a study participant went to bed before midnight (the bed time on the weekend (SOwkend) ≤ 1440 minutes), then

   MSF= (WTwkend -((1440- SOwkend+WTwkend)/2))/60 (hours),

   where WTwkend - wake time on the weekend;

b. If a study participant went to bed after midnight (SOwkend >1440 minutes), then
   MSF=(WTwkend -((WTwkend -(SOwkend -1440))/2))/60 (hours)

The MSF was corrected for make-up sleep on free days (weekends in this study) (MSFsc)[8]. The "oversleep" is an excessive time spent asleep on a weekend to compensate for sleep deprivation during the working week. The MSFsc was calculated using the formula:

MSFsc = MSF - (SDwkend - SD)/2,

where SDwkend – sleep duration on free days (weekend);

SD – average sleep duration across the week (includes sleep duration on all available week and weekend nights).

The MSF is adjusted for make-up sleep only in study participants who sleep longer on free days (weekend) than on work days. In persons who sleep longer on work days, chronotype is defined as MSF:

MSFsc = MSF

APPENDIX B:

Chronotype, Social Jetlag, Mood and Stress

In adjusted analyses, chronotype was not associated with mood and stress. Later chronotypes were associated with reduced risk of having bad sleep assessed with PSQI (Table B.1). Per 1 hour increase in lateness of chronotype, odds of bad sleep decreased 0.8 times (95%CI: 0.74-0.97).

Absolute SJL was not associated with TMD score and any of its six factors (Table B.2). Per 1 hour increase in absolute SJL risk of high perceived stress decreased 0.8 times (95%CI: 0.68-0.99). Stratification by latent chronotype group showed that among those with intermediate chronotypes, Per 1 hour increase in SJL, odds of high stress decreased 0.7 times (95%CI: 0.57-0.94, $p_{interaction}$=0.44).

Table B.1 Relationships between Chronotype, Mood, Stress, and Sleep Quality

Variable	Estimate	SE	p-value
TMD score (cont.)			
crude	0.03734	0.03488	0.29
adjusted[1]	0.007626	0.03528	0.83
Depression			
crude	0.02625	0.03647	0.47
adjusted[2]	-0.02261	0.03855	0.56
Tension-Anxiety			
crude	0.04439	0.02123	0.04
Adjusted[3]	0.01998	0.02140	0.35
Fatigue			
crude	0.02463	0.02163	0.26
Adjusted[4]	0.01687	0.02217	0.45
Confusion-bewilderment			
crude	0.03226	0.01760	0.07
Adjusted[5]	0.009604	0.01813	0.60
Anger-Hostility			
crude	0.02940	0.02826	0.30
Adjusted[6]	0.003888	0.02857	0.89
Vigor			
crude	-0.2096	-0.2096	0.19
Adjusted[7]	-0.2250	0.1557	0.15
PSS (cont.)			
crude	0.07438	0.1343	0.58
Adjusted[8]	-0.04034	0.1335	0.76
	OR	**95%CI**	**p-value**
PSS (>12 vs. ≤12)			
crude	1.04	0.93-1.17	0.51
adjusted[9]	1.01	0.88-1.13	0.98
PSQI (>5 vs. ≤5)			
crude	0.86	0.75-0.98	0.02
Adjusted[10]	0.84	0.74-0.97	0.01

Detailed legend: Linear models with repeated measures and unstructured correlation matrix (proc GLIMMIX). POMs, depression, tension modeled using lognormal distribution, vigor and PSS score - normal distribution for continuous variable). Dichotomous PSS score and PSQI were modeled with binary distribution).

[1] Adjusted for time, employment status, income, marital status, e-DII (continuous), sleep duration on work days, social desirability score, bulimia score, physical activity (continuous, MET-hrs), nap (yes/no)and

perceived body image.
[2] Adjusted for time, age, sex, alcohol, income, marital status, season, sleep duration on work days, race, bulimia score, social desirability score and perceived body image.
[3] Adjusted for time, age, e-DII (cont.), employment status, social desirability score, thinness score.
[4] Adjusted for time, race, season, alcohol, e-DII (cont.),sleep duration on work days, social desirability score, perceived body image and having children.
[5] Adjusted for time, income, race, marital status, e-DII (cont.), social desirability score, bulimia score.
[6] Adjusted for time, season, income, sleep duration on work days, desirability score, thinness score, ideal body image and current diet.
[7] Adjusted for time, sex, having children, physical activity (continuous, hrs), e-DII continuous), social desirability score, smoking status.
[8] Adjusted for time, age, sex, total sleep hours week day, physical activity hours, e-DII, income, season, social desirability score, bulimia score.
[9] Adjusted for time, sex, race, total number of hours slept on week night, e-DII (cont.), social desirability score, bulimia score.
[10] Adjusted for time, sleep duration on work days, social desirability score, bulimia score.

Table B.2 Relationships between Absolute Social Jetlag and Mood, Stress, and Poor Sleep

Variable	Estimate	SE	p-value
TMD score (cont.)			
crude	-0.08584	0.05492	0.12
adjusted[1]	-0.07980	0.05370	0.14
Depression			
crude	-0.05808	0.05894	0.33
adjusted[2]	-0.02329	0.05671	0.68
Tension-Anxiety			
crude	-0.02087	0.03014	0.49
Adjusted[3]	-0.01880	0.02931	0.52
Fatigue			
crude	0.004596	0.03160	0.88
Adjusted[4]	-0.02227	0.03103	0.47
Confusion-bewilderment			
crude	-0.03416	0.02523	0.18
Adjusted[5]	-0.04562	0.02455	0.06
Anger-Hostility			
crude	-0.00995	0.04115	0.81
Adjusted[6]	-0.02826	0.04033	0.48
Vigor			
crude	-0.09702	0.2236	0.66
Adjusted[7]	0.01722	0.2153	0.94
PSS (cont.)			
crude	-0.4022	0.1835	0.03
Adjusted[8]	-0.4906	0.1792	0.01
	OR	**95%CI**	
PSS (>12 vs. ≤12)			
crude	0.87	0.73-1.05	0.14
adjusted[9]	0.82	0.68-0.99	0.04
Stratified by latent chronotype group ($p_{interaction}=0.44$)[10]			
Early	1.05	0.68-1.60	0.83
Intermediate	0.73	0.57-0.94	0.02
Late	0.81	0.42-1.54	0.51
PSQI (>5 vs. ≤5)			
crude	0.91	0.75-1.11	0.37
Adjusted[11]	0.92	0.75-1.12	0.40

Detailed legend: Linear models with repeated measures and unstructured correlation matrix (proc GLIMMIX). TMD score, depression, tension modeled using lognormal distribution, vigor and PSS - normal distribution. [1] Adjusted for time, employment, sleep duration on work days, social desirability score, bulimia score. [2] Adjusted for time, sex, race, income,

marital status, season, sleep duration on work days, alcohol, caffeine (tertiles), bulimia score and perceived body image. [3] Adjusted for time, income, e-DII (cont.), employment, social desirability score and thinness score. [4] Adjusted for time, race, e-DII, sleep duration on work days, social desirability score, perceived body image, having children. [5] Adjusted for time, marital status, total sleep duration on work days, social desirability score, bulimia score. [6] Adjusted for time, season, current diet, social desirability score, thinness score, ideal body image, sleep duration on work days. [7] Adjusted for time, sex, physical activity (continuous, hrs),social desirability score, having children, smoking status. [8] Adjusted for `time`, sex, total sleep duration on work days (cont., hrs), e-DII (cont.), income, season, social desirability score, bulimia score. [9] Adjusted for time, sex, race, e-DII (cont.), total sleep duration on work days, social desirability score, bulimia score. [10] Adjusted for time, sex, race, e-DII (cont.), total sleep duration on work days, social desirability score, bulimia score. [11] Adjusted for time, marital status, social desirability score and thinness score.