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Circadian misalignment, or “social jetlag” refers to a mismatch between the internal circadian clock and external timings (e.g. societal timings) and behaviorally manifests as inappropriately timed sleep/wake cycles or misalignment of sleep patterns with meal timings. Previous literature shows circadian misalignment to contribute to a large number of adverse health outcomes including metabolic changes and disorders, mood disturbance, and decreased daytime functioning. A number of the adverse health outcomes of circadian misalignment, such as depression, suicidality, and burnout are all common within the medical student population. Medical students also tend to exhibit behaviors which promote circadian misalignment, such as staying up late to study, pulling all-nighters for exams, and sleeping in on weekends. Despite these links, very little literature exists regarding the prevalence, manifestations, and effects of circadian misalignment on medical students. This study identifies key behaviors related to circadian misalignment in medical students, as well as identifying negative outcomes associated with these behaviors.

THE IMPACT OF CIRCADIAN MISALIGNMENT

ON HEALTH AND WELLNESS IN

MEDICAL STUDENTS

RESEARCH PRACTICUM REPORT

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CHAPTER I

INTRODUCTION

Medical students are highly vulnerable to circadian misalignment, which refers to a mismatch in timing between their master internal circadian clock and societally-imposed clocks. Irregular sleep behaviors common in medical students such as staying up late to study for exams and inconsistent wake times strongly promote circadian misalignment. Furthermore, dietary and metabolic factors including meal influence circadian misalignment. Circadian misalignment negatively impacts mood and cognitive performance, two areas of critical importance in the medical school student population as evidenced by the staggering rates of suicidality among medical students. Despite medical students' increased vulnerability to both circadian misalignment and its adverse outcomes, few studies have examined the role circadian misalignment and its promoting behaviors play in these outcomes for this population. We sought to gain a better understanding of how circadian misalignment presents in medical students by investigating the relationship between the sleep and eating behaviors that promote circadian misalignment and adverse outcomes. This study inspected this relationship of sleep patterns and meal timings by examining these behaviors in first and second year medical students enrolled in the Texas College of Osteopathic Medicine at the University of North Texas Health Science Center. Results showed circadian misalignment contributes to adverse health and wellness outcomes including increased sleep inertia, decreased sleep efficiency, sleep restriction, and

depressed mood symptoms. Misaligned students differed significantly from their aligned peers in several areas including sleep efficiency, wake time, phase preference, and meal window. Multiple behaviors associated with circadian misalignment, such as time in bed and waketime, also predicted mood and sleep inertia. These data demonstrate that circadian misalignment results in a positive feedback loop wherein misaligned students engage in behaviors that delay first light exposure and meal timings, thereby maintaining misalignment.   Our results suggest further research is needed in order to inform both medical students and medical institutions as well as allow for the development of preventative and interventive strategies.

CHAPTER II

PROBLEM/HYPOTHESIS

Circadian misalignment, also known as "social jetlag," refers to a mismatch between the internal circadian clock and external timings (e.g., societal timings like school start time) and behaviorally manifests as inappropriately timed sleep/wake cycles or misalignment of sleep patterns with meal timings (Baron & Reid, 2014). Previous literature shows that circadian misalignment contributes to metabolic changes and disorders, mood disturbance, and increased daytime dysfunction such as increased daytime sleepiness and decreased cognitive performance (Baron & Reid, 2014; Chellappa, Morris, & Scheer, 2018). Mistimed sleep/wake cycles are frequently a result of insufficient sleep durations, irregular sleep patterns, and delayed sleep/wake timing (Baron & Reid, 2014). Situational factors such as shift work as well as personal factors such as genetics and chronotype (circadian phase preference) can also promote circadian misalignment (Mahoney, 2010; Shi, Wu, Ptacek, & Fu, 2017; Vitale et al., 2015). Further still, while nychthermal light/dark cycles are the most important mechanism of entrainment of the circadian clock, eating patterns are closely linked to circadian rhythms. For instance, literature has shown that a delayed first meal alters hepatic circadian oscillation and induces lipid abnormalities in rats (Shimizu et al., 2018). Though this close connection exists between these two behavioral aspects of circadian misalignment, few studies have adequately examined how sleep and meal timing may synergistically impact adverse health outcomes that both independently promote. Medical students are a particularly vulnerable population due to numerous factors, including their age placing these students at the tail end of adolescence and a notoriously high time requirement for coursework. Despite their increased vulnerability, few studies of circadian misalignment have been conducted in medical school populations.

To address this critical need, our overall objectives were to (1) identify how circadian misalignment behaviorally manifests in medical students as measured by sleep and eating patterns, and (2) determine how the behavioral patterns of sleeping and eating impact mood, daytime functioning, and academic performance. We hypothesized that greater variability in sleep and meal timings will independently increase the likelihood and severity of depressed mood and result in poorer academic performance. We further hypothesized that the presence of variability in both sleep patterns and meal timing will have a more deleterious effect on measured outcomes compared to the independent effect of each factor.

SIGNIFICANCE

The rationale for this analysis is that a better understanding of how circadian misalignment manifests in medical students will inform prevention and intervention strategies to reduce its adverse impact on their health and wellbeing. Medical students are at high risk for suicidality, mental health conditions, and burnout (Mazurkiewicz, Korenstein, Fallar, & Ripp, 2012; V. Silva et al., 2017). Circadian misalignment contributes to the occurrence of all of these adverse outcomes (Costa, 2010; Pagnin & de Queiroz, 2015). Therefore, it is of the utmost importance to identify how circadian misalignment manifests in the sleep and meal patterns of medical students, and to determine what role these behavioral patterns that promote circadian misalignment play in depressed mood symptoms, daytime dysfunction, and academic performance in this population.

BACKGROUND

Objective 1: Identify how circadian misalignment behaviorally manifests in medical students as measured by sleep and eating patterns

Circadian misalignment, as mentioned above, refers to the mismatch between the internal master circadian clock and external timings (such as societal timings), which behaviorally manifests as inappropriately timed sleep/wake cycles or misalignment of sleep patterns with meal timings (Baron & Reid, 2014).

Inappropriately timed sleep/wake cycles are often caused by insufficient sleep durations, irregular sleep patterns, and delayed sleep timing. In addition, circadian phase preference, or chronotype, (Vitale et al., 2015) and genetics influence sleep timing (Ashbrook, Krystal, Fu, & Ptacek, 2019; Juda, Vetter, & Roenneberg, 2013; Shi et al., 2017; Soehner, Kennedy, & Monk, 2011). Chronotype refers to preferred sleep timing and is typically categorized as morning ("morning lark"), intermediate, and evening ("night owl") type. Individuals with a strong morning or evening type preference can experience more severe difficulties as their internal timing differs from societal timing (Murray et al., 2017). However, evening types typically fair worse as their internal clock does not promote an early-to-rise lifestyle.

An example of a deleterious outcome associated with strong evening preference is Delayed Sleep Phase Disorder (DSPD), a condition characterized by a strong evening preference that mirrors a delayed internal circadian timing. Consequently, these individuals experience sleep onset insomnia when attempting to fall asleep before their internally preferred (circadian) time, and an inability to spontaneously rise earlier than their internally preferred time. Traditionally, an individual with DSPD will not display these sleep and wake difficulties when allowed to follow their internally preferred schedule (Alvarez, Dahlitz, Vignau, & Parkes, 1992). DSPD strongly promotes circadian misalignment. Individuals who experience this condition will either attempt to sleep during their biological day, which differs from societal timing, or dramatically reduce their total sleep timing in order to conform to societally necessitated timings. Individuals with DSPD may also further dysregulate themselves by napping or sleeping in on the weekends in an attempt to "catch up on sleep." This dysregulating behavior of restricted weekday sleep combined with oversleeping on weekends is also evident in non-DSPD populations, such as adolescents and young adults (Crowley & Carskadon, 2010).

Behaviors that support regularity such as consistent social cues from a roommate or partner, consistent sleep/wake timings, and consistent meal timings will promote circadian alignment, while behaviors that disrupt regularity will promote circadian misalignment. As shown in Figure 1, when isolated from external cues, the circadian rhythm tends to "free run" and individuals exhibit a gradually delaying pattern of sleep timing (Kronauer, Czeisler, Pilato, Moore-Ede, & Weitzman, 1982). Kronauer et al. (1982) demonstrated this through studies of individuals who were isolated from external temporal cues. The propensity to free run is due to the internal master circadian clock lasting slightly longer than one 24-hour day on Earth, with an average duration of roughly 24.4 hours (Kronauer et al., 1982). In the standard individual this "free running" is entrained by external zeitgebers such as meal time, physical/social activity, and most importantly, light (Baron & Reid, 2014).

Further impacting the influence of these external cues are relationships that exist between them. Circadian misalignment and factors that promote it, such as sleep timing and chronotype, have been found to influence both when eating occurs and what is eaten (C. M. Silva et al., 2016). For instance, evening type circadian preference predicts skipping breakfast (Reutrakul et al., 2014). In addition, sleep timing has also been shown to influence caloric intake, and was independently associated with calories consumed after 20:00 (Baron, Reid, Kern, & Zee, 2011). It has also been demonstrated that delayed first active-phase meal (such as could be found by skipping breakfast) induces abnormal metabolism and disruption of the hepatic circadian clock in rats (Shimizu et al., 2018). Research also shows that late-night eating promotes circadian misalignment (Ni et al., 2019).

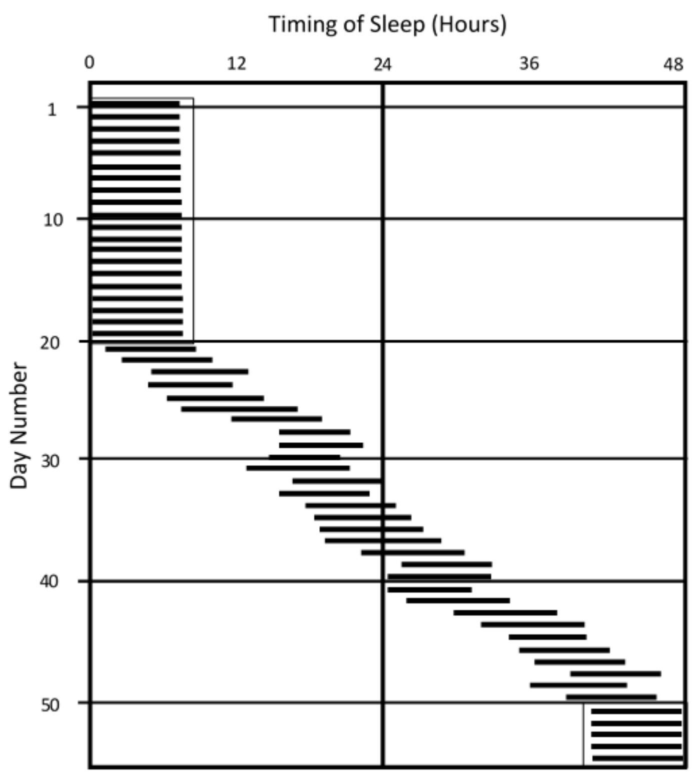

Figure 1. Figure 1 is a generated example of free running vs. entrainment based on a 1981 study by Czeisler et al. (Czeisler et al., 1981).

Within the body, circadian misalignment is also characterized by an internal dysregulation between the master circadian clock and peripheral clocks. The master circadian clock is coordinated in the suprachiasmatic nucleus (SCN), located in the hypothalamus. As shown in Figure 2, the master clock plays a prominent role in many aspects of physiology – the most easily observable of these, and perhaps the most important, is sleep and hormone release (Baron & Reid, 2014). One such hormone, melatonin, serves as an endogenous marker of the intrinsic circadian clock.

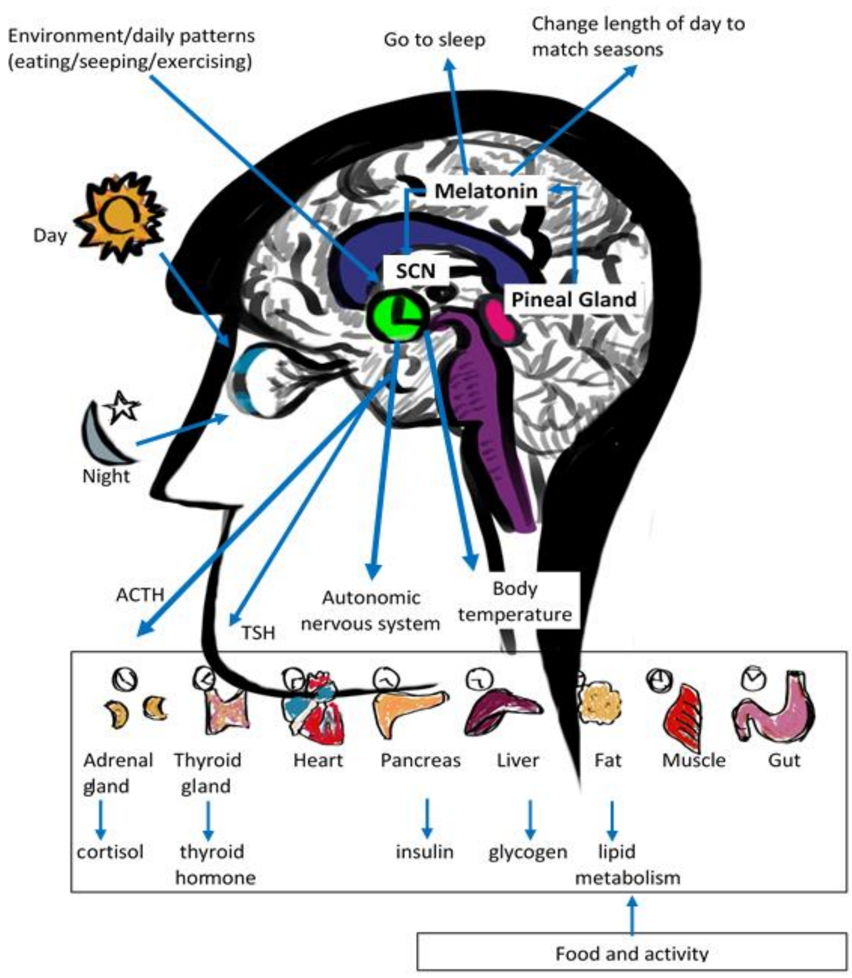

Figure 2. Figure 2, based on a figure from Hickie et al. (2013), shows the master clock and its relation to the peripheral clocks and zeitgebers (Hickie et al., 2013).

Melatonin is produced in the pineal gland and therefore outside of the blood brain barrier (BBB) (Pereira, Pradella Hallinan, & Alves, 2017). Melatonin (N-acetyl-5-methoxytryptophan) is a downstream derivative of both the essential amino acid tryptophan (TRP) and serotonin (5-hydroxytriptamine, or 5-HT). In order for TRP to be converted to 5-HT, it must be actively transported across the BBB to the raphe nucleus where 5-HT is produced. The carrier that transports TRP across the BBB is also utilized by other large neutral amino acids (leucine, isoleucine, tyrosine, etc.), and competition exists between these various amino acids for entry to the brain. During the daytime, when melatonin is not being produced, TRP more easily passes through the BBB because the ratio of TRP to other competing amino acids that utilize the same trans-BBB transported is high. Increased production of melatonin at night in the pineal gland, which directly uptakes TRP to convert it to melatonin, results in decreased availability of TRP for transport. Reduced TRP availability decreases the ratio of TRP to other competing amino acids and, thereby, decreases the likelihood it will be transported to the serotonergic neurons within the BBB. As such, synthesis of 5-HT is decreased (Pereira et al., 2017).

Increased melatonin, or delayed offset of melatonin, also impacts the gastrointestinal (GI) system. SERT, the serotonin transporter responsible for reuptake of 5-HT, is inhibited by melatonin (Matheus, Mendoza, Iceta, Mesonero, & Alcalde, 2010). The majority of the body's 5-HT receptors are located in the gut. One of the primary roles of 5-HT in the GI system is increased intestinal motility (Camilleri, 2009). Additionally, the 5-HT_3 receptor stimulates nausea and vomiting (Canziani et al., 2018). Later offset of melatonin production promotes later offset in the inhibition of SERT by still-active melatonin, which increases the likelihood of waking with GI upset and/or nausea. The induced nausea or other GI upset likely results in an increased propensity for individuals with DSPD and others who experience a delayed preference to skip breakfast, and thereby further promote circadian misalignment.

Research with DSPD demonstrates behavioral patterns alter melatonin timing and suggests these same physiological mechanisms underlie adverse outcomes individuals who experience circadian misalignment. While not required for diagnosis, DSPD is commonly associated with delayed onset of melatonin as measured by Dim Light Melatonin Onset (DLMO). This delayed melatonin onset and offset for individuals with DSPD may be, in part, due to a genetic predisposition for DSPD via a coding variation in CRY1 (Patke et al., 2017). However, a delay in melatonin timing is also strongly influenced by behavioral patterns like irregular sleep/wake times. Such irregular sleep/wake patterns are often the result of sleep behaviors such as sleeping in on the weekends (thus delaying first light exposure and thereby melatonin offset) or staying up late to study (delaying onset of melatonin production)and are evident in medical student populations (Lima, Medeiros, & Araujo, 2002).

Objective 2: Determine how these sleeping and eating behavioral patterns impact mood and daytime functioning

Melatonin and serotonin share a bidirectional relationship in that production of melatonin is directly dependent on 5-HT. As mentioned above, melatonin directly inhibits both the conversion of L-tryptophan to 5-HT within the BBB as well as SERT. SERT is the main target of the class of antidepressants known as Selective Serotonin Reuptake Inhibitors, or SSRIs (Beikmann, 2014). An inhibition is beneficial during the daytime; however, delay in melatonin offset in the morning would then promote decreased 5-HT upon waking, which would promote depressed mood. As such, circadian misalignment and behaviors that promote it are associated with increased depressive symptoms (Murray et al., 2017).

This same physiological relationship between serotonin, melatonin, and the essential amino acid TRP implies that meal timings may also play a role in mood. The inhibiting effects of melatonin on 5-HT production suggests that the increased caloric intake near bedtime in individuals exhibiting delayed sleep patterns will not promote the same levels of 5-HT production as would be found for an equal caloric intake shortly after wake time. Consequently, delayed meal timing appears to also contribute to increased depressive symptoms (Baron et al., 2011).

Beyond depression, it has also been shown that daily circadian misalignment promotes decreased sustained attention and cognitive performance (e.g. information processing, visual-motor performance). Sleep inertia, a state in which an individual experiences impaired cognitive performance upon wake, is also significantly greater during the biological night (Scheer, Shea, Hilton, & Shea, 2008). Individuals with circadian misalignment are more inclined to experience sleep inertia due to societally necessitated wake times occurring during their endogenous night (Burke, Scheer, Ronda, Czeisler, & Wright, 2015; Ritchie et al., 2017). In addition, although misaligned individuals felt sleepier, they did not rate their performance as worse (Chellappa et al., 2018). Their ratings suggest that these individuals experience low self-awareness of the adverse impact their sleep patterns had on their performance, which means they are more likely to continue engaging in behaviors that adversely impact them. Daytime functioning such as attendance to class with active participation and studying may also be dramatically inhibited, impairing the ability of misaligned individuals to prepare for and perform well on exams. For medical students, this may lead to dramatically reduced cognitive performance for early morning classes and homework completion as they prepare for exams. Furthermore, circadian misalignment influences daytime function in the form of decreased physical activity and disturbed immune functioning that increases likelihood of being sick or ill (Labrecque & Cermakian, 2015; Yamanaka, 2006).

RESEARCH DESIGN AND METHODS

Population

The conducted study utilized archival data from an experimental study that examined sleep in medical students (PI: Dr. Brandy Roane). Inclusion criteria for the larger study required participants to be eighteen years or older and be enrolled at the Texas College of Osteopathic Medicine at the University of North Texas Health Science Center as either first or second year medical student at the time of the study. Current analysis required the additional inclusion criteria of completing at least two daily records, of which one must be for a school day and one must be for a non-school day. Individuals will be excluded based on the presence of obstructive sleep apnea (OSA) symptoms.

Study Design

Data collection occurred during the fall and spring semesters of the 2016-2017 and 2017-2018 academic years. Students were recruited via email announcement and provided electronic consent prior to enrollment in the study. The study was approved by the Institutional Review Board of the University of North Texas Health Science Center. Participants completed an initial online survey designed to capture sleep health and behaviors, sleep disorder symptoms, and demographic characteristics such as age, race/ethnicity, and gender. Once the initial survey was received, students were asked to complete three daily records within the next two weeks (two school days, one non-school day). Daily records obtained information on daily sleep and health behavior. Analysis examined data from the initial survey and daily records.

Measures

Circadian misalignment. Self-reported sleep patterns were captured by the Adolescent Sleep Hygiene Scale (ASHS) on the initial survey (LeBourgeois, Giannotti, Cortesi, Wolfson, & Harsh, 2005; Storfer-Isser, Lebourgeois, Harsh, Tompsett, & Redline, 2013). Students reported on their typical bedtime and wake time for school and non-school days. Circadian misalignment is reflected behaviorally by a mismatch in sleep timing of 90 minutes or more (Baron & Reid, 2014). For the current analysis, students who reported a difference of 90 minutes or more between the school and non-school day wake time met criteria for **circadian misalignment**.

Sleep patterns. Students completed two to three daily records on school (one to two records) and non-school (one record) days. Means and standard deviations for school and non-school days were calculated from the daily records for bedtime (sleep onset initiating the sleep period), wake time (sleep offset ending the sleep period), total time in bed (time of getting into bed to time of getting out of bed), sleep duration (total time in bed minus time awake in bed), sleep efficiency (percent of time spent asleep during total time in bed), night wakings (number of times wakefulness occurred in the sleep period), and wake after sleep onset (WASO, total time spent awake after initiating sleep for the first time during the sleep period).

Sleep measures. As part of the initial survey participants completed the Composite Scale of Morningness, CS, (Smith, Reilly, & Midkiff, 1989) capturing their phase preference. Participants also completed the Epworth Sleepiness Scale, ESS, which captures daytime sleepiness (Johns, 1991). Obstructive Sleep Apnea (OSA) was ruled out via STOP-Bang questionnaire (Chung et al., 2008).

Eating patterns. Daily records captured the timing for first and last meals (hour and minute) as well as size of each meal (small, medium large).

Daytime functioning. Daily records also captured if students were sick (yes/no), had school (yes/no), completed course work and homework (durations in minutes), and engaged in physical activity (duration in minutes). Number of naps taken as well as nap duration (duration in minutes) was also captured on daily records. Students further reported on experiencing sleep inertia via a rating on how refreshed they felt upon waking (scale: -5 for "very tired" to +5 for "wide awake").

Mood. Students reported on their mood via the daily record (scale: -5 "very poor" to +5 "great").

Data analysis

To achieve Objective 1, univariate ANOVAs were conducted to determine significant differences between students in the circadian aligned and misaligned groups for demographic variables (age, sex, race/ethnicity, academic year), covariate sleep-related variables (chronotype, daytime sleepiness), sleep patterns (mean sleep duration, mean sleep timing, sleep duration variability, sleep timing variability), and meal patterns (mean eating period duration, mean meal timing, eating period variability, meal timing variability).

To achieve Objective 2 and test the first hypothesis, univariate ANOVAs were conducted to determine significant differences between students in the circadian aligned and misaligned groups for the dependent variables of daytime functioning (days sick, coursework, homework, physical activity, napping, sleep inertia) and mood. To test the second hypothesis, multiple regression analysis was conducted to determine how sleep and eating patterns predict daytime functioning and mood.

RESULTS

Objective 1: Identify how circadian misalignment behaviorally manifests in medical students as measured by sleep and eating patterns

Demographics

Participants included 107 first- and second-year medical students (62.6% 1st year) who provided data on gender, race/ethnicity, and age. Mean age was 24.6 years (SD = 2.5 years). Participants were 66.4% female and 51.4% Caucasian, 36.4% Asian, and 12.2% other (Table 1). Of the 107 students, 70 (65%) met the study criteria of circadian misalignment (i.e., students reporting >90-minute difference in bedtime or waketime from school to non-school nights). Chi-square and univariate analyses showed no group differences for the demographic variables.

Sleep and Eating Patterns

Sleep disorder symptoms. In addition to demographic variables, Table 1 displays means and standard deviations for sleep disorder symptoms. Univariate analyses showed a significant difference in phase preference scores between students identified as circadian misaligned and those who were aligned, F (1, 105) = 19.1, *p* <0.001. Statistically significant differences were not present for daytime sleepiness, apnea symptoms, and insomnia symptoms.

Table 1. Unadjusted univariate ANOVA Analyses by Group for Demographics with Mean(Standard Deviation).

	All	Circadian Misaligned	Circadian Aligned	X^2	p
Gender	107	70	37	0.06	0.813
Female	71	47	24		
Male	36	23	13		
Race/Ethnicity	107	70	37	6.11	0.295
Asian	39	26	13		
Black / African American	1	0	1		
Hispanic	4	4	0		

Caucasian	55	35	20		
Other	1	0	1		
Multiracial	7	5	2		
Academic year (1st year)	107	70	37	0.83	0.362
First year	67	46	21		
Second year	40	24	16		
	All	**Circadian Misaligned**	**Circadian Aligned**	**F**	**p**
Age	24.6	24.4	25.1	1.62	0.206
Phase preference*	34.1	31.9	38.2	19.13	<0.001
Insomnia symptoms	9.1	9.3	8.5	1.25	0.266
Sleep apnea symptoms	0.9	1	0.9	0.51	0.477

*Parameter estimates significant at $p < 0.05$.

Sleep patterns and meal timing. For sleep patterns, unadjusted univariate ANOVA analyses (see Table 2) found statistically significant group differences in school day waketime (misaligned = 07:30 versus aligned = 06:54) and sleep efficiency (misaligned = 82.2% versus aligned = 88.5%) and a trend differences in school day time out of bed (misaligned = 07:54 versus 07:20).

Table 2. Unadjusted univariate ANOVA Analyses by Group for Sleep Patterns with Mean(Standard Deviation).

	All	**Circadian Misaligned**	**Circadian Aligned**	**F**	**p**
School Nights					
Total time in bed (minutes)	467.9 (105.5)	478.6 (104.6)	447.6 (105.6)	2.05	0.155
Sleep duration (minutes)	400.3 (97.2)	394.3 (106.2)	412.2 (76.7)	0.77	0.383
In bed (24-hour, minutes)	23:48 (78)	23:48 (78)	23:42 (90)	0.41	0.522
Bedtime (24-hour, minutes)	00:18 (90)	00:30 (90)	00:00 (90)	2.34	0.129
Waketime (24-hour, minutes)**	**07:18 (84)**	**07:30 (90)**	**06:54 (72)**	**4.19**	**0.043**

Out of bed (24-hour, minutes)**	**07:42 (84)**	**07:54 (90)**	**07:18 (78)**	**3.9**	**0.051**
Sleep efficiency (percent)*	**84.3% (13.4%)**	**82.2% (14.9%)**	**88.5% (6.9%)**	**5.46**	**0.022**
Non-school Nights					
Total time in bed (minutes)	491.7 (94.2)	497.7 (101.5)	481.1 (79.8)	0.73	0.395
Sleep duration (minutes)	413.1 (99.1)	414.1 (98.9)	411.2 (101)	0.02	0.891
In bed (24-hour, minutes)	00:06 (108)	00:12 (108)	23:54 (108)	0.93	0.338
Bedtime (24-hour, minutes)**	**00:36 (102)**	**00:48 (96)**	**00:06 (102)**	**3.85**	**0.052**
Waketime (24-hour, minutes)*	**07:54 (96)**	**08:06 (90)**	**07:24 (102)**	**4.6**	**0.034**
Out of bed (24-hour, minutes)*	**08:18 (96)**	**08:30 (90)**	**07:54 (108)**	**3.62**	**0.06**
Sleep efficiency (percent)	84.4% (13.5%)	83.7% (11.7%)	85.8% (16.5%)	0.55	0.462
Non-school to School Nights					
Total time in bed (minutes)	23 (139.6)	18.3 (150.5)	31.4 (119.4)	0.2	0.654
Sleep duration (minutes)	12.1 (130.3)	19.5 (140.2)	-2.6 (108.9)	0.61	0.437
In bed (minutes)	18 (102)	24 (108)	12 (90)	0.3	0.588
Bedtime (minutes)	18 (84)	24 (90)	12 (84)	0.47	0.494
Waketime (minutes)	30 (114)	36 (114)	30 (108)	0.05	0.82
Out of bed (minutes)	36 (120)	36 (2)	36 (114)	0.03	0.866
Sleep efficiency (percent)	0.2% (18%)	1.6% (17.3%)	-2.7% (19.3)	1.2	0.274

*Parameter estimates significant at $p < 0.05$; **Parameter estimates significant at $p < 0.1$.
Note. Positive values = Non-school > School. Negative values = Non-school < School.

Statistically significant group differences were found in non-school day waketime (misaligned = 08:06 versus aligned = 07:24) and trend differences in non-school day bedtime (misaligned = 00:48 versus aligned = 00:06) and time out of bed (misaligned = 08:30 versus aligned = 07:54). No statistically significant differences were found between groups for sleep pattern variability.

For meal timing, unadjusted univariate ANOVA analyses (see Table 3) found statistically significant group differences in total meal period variability from school to non-school days (misaligned = -80.2 minutes versus aligned = 13 minutes). No other statistically significant group differences were found for meal timing.

Table 3. Unadjusted univariate ANOVA Analyses by Group for Meal Patterns with Mean(Standard Deviation).

	All	**Circadian Misaligned**	**Circadian Aligned**	**F**	**p**
School Nights					
Breakfast (24-hour, minutes)	08:36 (84)	08:42 (90)	08:30 (78)	0.76	0.384
Dinner (24-hour minutes)	18:36 (102)	18:36 (120)	18:42 (60)	0.1	0.756
Total meal period (minutes)	592.1 (143.6)	600.5 (147.7)	577 (136.8)	0.58	0.448
Non-school Nights					
Breakfast (24-hour, minutes)	09:24 (114)	09:30 (84)	09:24 (156)	0.08	0.773
Dinner (24-hour, minutes)	18:54 (78)	19:00 (78)	18:36 (72)	1.89	0.172
Total meal period (minutes)	579.8 (144.3)	573.6 (122)	589.2 (174.9)	0.23	0.631
Non-school to School Nights					
Breakfast (minutes)	42 (126)	42 (114)	54 (2.4)	0.28	0.6
Dinner (minutes)	12 (90)	20 (108)	-1.2 (48)	0.92	0.341
Total meal period (minutes)*	**-47.8 (220.9)**	**-80.2 (218.1)**	**13 (216.4)**	**4.08**	**0.046**

*Parameter estimates significant at p < 0.05.
Note. Positive values = Non-school > School. Negative values = Non-school < School.

Univariate ANCOVA analyses adjusting for age, gender, race, medical school year, phase preference, and daytime sleepiness (see Table 4) found no statistically significant group differences in sleep patterns and meal timing for school and non-school night or variability in their timing. Trend differences were found in non-school night time in bed, $F(1, 101) = 2.82$, $p = 0.096$.

Table 4. ANCOVA Analyses by Group for Daytime Functioning with Mean(Standard Deviation).

	All	**Circadian Misaligned**	**Circadian Aligned**	**F^**	**p**
School Nights					
Coursework (minutes)	161.9 (150.7)	171.3 (152.5)	144 (147.8)	0.84	0.361
Homework (minutes)	178.1 (160.8)	166 (143.5)	202.6 (191.4)	0.73	0.395
Sick (days)	0.4 (0.2)	0.04 (0.2)	0.04 (0.2)	0.23	0.630
Physical activity (minutes)	12 (20.9)	11.3 (20.4)	13.4 (22.2)	0.01	0.94
Napping (minutes)	15.7 (28.9)	18.4 (31.2)	10.8 (23.7)	0	0.986
Sleep inertia (rating)	6.9 (2.3)	6.6 (2.4)	7.6 (2)	0.95	0.333
Mood (rating)	7.8 (2)	7.5 (2)	8.3 (1.9)	1.73	0.191
Non-school Nights					
Coursework (minutes)	127 (152)	130.8 (140.5)	118.7 (178.2)	0.01	0.914
Homework (minutes)	182.7 (202.3)	187.6 (198.7)	172.8 (212.7)	0.08	0.781
Sick (days)	0.1 (0.2)	0.06 (0.2)	0.04 (0.2)	0.47	0.495
Physical activity (minutes)	13.3 (40.2)	15 (47.3)	10.2 (21.8)	0.05	0.817
Napping (minutes)*	**20.2 (44.5)**	**28.5 (52.6)**	**5.1 (14.3)**	**4.49**	**0.037**
Sleep inertia (rating)	7.3 (2.4)	`7.3 (2.5)	7.3 (2.2)	0.15	0.701
Mood (rating)	7.9 (2.3)	7.8 (2.4)	8.1 (2)	0.14	0.713

^Models adjusted for age, gender, race/ethnicity, medical school year, phase preference, and daytime sleepiness.
*Parameter estimates significant at $p < 0.05$.

Objective 2: Determine how these sleeping and eating behavioral patterns impact mood and daytime functioning.

Impact of Circadian Misalignment, Sleep Patterns, and Meal Timing on Daytime Functioning

Table 5. Multiple Regression Analyses with Sleep Patterns Predicting Daytime Functioning.

	Adjusted R Square	**R^2 Change**	**F^**	**p**
School Nights				
Coursework (minutes)	0.04	0.14	1.37	0.208
Homework (minutes)	-0.03	0.09	0.77	0.654
Sick (days)*	**0.15**	**0.23**	**2.79**	**0.005**
Physical activity (minutes)**	**0.06**	**0.16**	**1.69**	**0.096**
Napping (minutes)*	**0.11**	**0.19**	**2.26**	**0.021**
Sleep inertia (rating)*	**0.2**	**0.28**	**3.66**	**<0.001**
Mood (rating)*	**0.09**	**0.18**	**2.02**	**0.04**
Non-school Nights				
Coursework (minutes)**	**0.08**	**0.19**	**1.72**	**0.093**
Homework (minutes)	-0.03	0.1	0.75	0.677
Sick (days)	-0.04	0.07	0.65	0.768
Physical activity (minutes)	0.07	0.16	1.67	0.101
Napping (minutes)*	**0.16**	**0.24**	**2.91**	**0.003**
Sleep inertia (rating)*	**0.14**	**0.22**	**2.57**	**0.009**
Mood (rating)	-0.04	0.06	0.61	0.801

^Models adjusted for age, gender, race/ethnicity, medical school year, phase preference, and daytime sleepiness.
*Parameter estimates significant at $p < 0.05$. **Parameter estimates significant at $p < 0.1$.

Circadian misalignment and daytime functioning. Univariate ANCOVA analyses adjusting for age, gender, race, medical school year, phase preference, and daytime sleepiness (see Table 5) found statistically significant group differences in napping on non-school days (misaligned = 28.5 versus aligned = 5.1). No statistically significant differences were found between groups for course work, homework, days sick, physical activity, napping, sleep inertia, or mood (see Table 4).

Table 6. Multiple Regression Analyses with Meal Timing Predicting Daytime Functioning.

	Adjusted R Square	**R^2 Change**	**F^**	**p**
School Nights				
Coursework (minutes)*	**0.12**	**0.21**	**2.31**	**0.024**
Homework (minutes)	-0.1	0.1	0.89	0.541
Sick (days)*	**0.16**	**0.24**	**3**	**0.004**
Physical activity (minutes)*	**0.09**	**0.18**	**2.03**	**0.046**
Napping (minutes)**	**0.07**	**0.16**	**1.77**	**0.087**
Sleep inertia (rating)*	**0.17**	**0.25**	**3.11**	**0.003**
Mood (rating)	0.06	0.15	1.61	0.125
Non-school Nights				
Coursework (minutes)	0.09	0.21	1.74	0.1
Homework (minutes)	-0.02	0.12	0.88	0.549
Sick (days)	-0.07	0.05	0.39	0.936
Physical activity (minutes)**	**0.1**	**0.2**	**1.92**	**0.063**
Napping (minutes)*	**0.08**	**0.18**	**1.82**	**0.08**
Sleep inertia (rating)	0.01	0.12	1.09	0.382
Mood (rating)	0.03	0.14	1.3	0.253

^Models adjusted for age, gender, race/ethnicity, medical school year, phase preference, and daytime sleepiness.
*Parameter estimates significant at $p < 0.05$. **Parameter estimates significant at $p < 0.1$.

Multiple regression analyses adjusting for age, gender, race, medical school year, phase preference, and daytime sleepiness (see Table 6) showed statistically significant models for school night course work, days sick, physical activity, napping, and sleep inertia. For non-school nights, models were statistically significant for physical activity and napping.

Sleep patterns and daytime functioning. Main effect analyses showed statistically significant predictors of sleep inertia on school days were bedtime (standardized β = -0.54, p = 0.015, 95 percentile Confidence Interval = -1.5 – -0.16), and out of bed time (standardized β = 0.7, p = 0.043, 95 percentile Confidence Interval = 0.4 – 2.2). Statistically significant predictors of school day mood were waketime (standardized β = -0.77, p = 0.035, 95 percentile Confidence Interval = -2.2 – -0.1) and time out of bed (standardized β = 0.97, p = 0.009, 95 percentile Confidence Interval = 0.4 – 2.4). Statistically significant predictors of naps on non-school days were time in bed (standardized β = -1.2, p < 0.001, 95 percentile Confidence Interval = -43.5 – -14.6) and bedtime (standardized β = 1.2, p < 0.001, 95 percentile Confidence Interval = 14.53 – 46.1). Waketime on non-school days was a statistically significant predictor of sleep inertia (standardized β = 1.1, p = 0.002, 95 percentile Confidence Interval = -0.21 – 65.2). Analyses also found trends for time out of bed on non-school days predicting sleep inertia (standardized β = -0.63, p = 0.064, 95 percentile Confidence Interval = -1.85 – 0.06), non-school night time in bed predicting sick days (standardized β = -0.59, p = 0.075, 95 percentile Confidence Interval = -0.14 – 0.01), and non-school night bedtime predicting physical activity (standardized β = -0.57, p = 0.085, 95 percentile Confidence Interval = -29.3 – 1.9).

Main effects for covariates with sleep patterns showed that on school days, age and gender were significant predictors of being sick, age and daytime sleepiness predicted physical activity, race/ethnicity and phase preference predicted sleep inertia, and phase preference predicted mood ratings. On non-school days, daytime sleepiness predicted physical activity.

Meal patterns and daytime functioning. Non-school day dinner time was a statistically significant predictor of napping (standardized β = 0.28, p = 0.035, 95 percentile Confidence Interval = 0.69 – 18.86). Analyses found trends for school day dinner timing predicting minutes spent on classwork (standardized β = 0.26, p = 0.051, 95 percentile Confidence Interval = -0.2 – 65.2), and meal eating period predicting mood (standardized β = 0.25, p = 0.082, 95 percentile Confidence Interval = -0.5 – 0.3).

Main effects for covariates with meal timing showed that on school days, age predicted minutes spent on classwork, age and gender predicted days sick, age and daytime sleepiness predicted physical activity, phase preference predicted napping, race/ethnicity and phase preference predicted sleep inertia, and race/ethnicity and daytime sleepiness predicted mood. On non-school days, age predicted minutes spent on classwork, daytime sleepiness predicted physical activity.

DISCUSSION

With regards to the first objective of this study, to identify how circadian misalignment behaviorally manifests in medical students as measured by sleep and eating patterns, our results are consistent with previous literature – i.e., misaligned individuals display longer meal windows, later meal offset timing, and later sleep/wake timings. The results of this study also suggest results in line with the hypothesis put forth by this study's second objective to determine how these sleeping and eating behavioral patterns impact mood and daytime functioning. Namely, behaviors which contribute to circadian misalignment also appear to contribute to both decreased daytime functioning as well as increased depressive mood. Based on previous literature we would expect circadian misalignment to decrease mood and physical activity, as well as increase the likelihood of being sick or ill (Labrecque & Cermakian, 2015; Yamanaka, 2006). Our results showed that circadian phase did in fact lead to depressed mood, and trend findings showed non-school bedtime predicted physical activity. Our results did not show any relation to time sick or ill, however this may have been due to how we measured sick (binary yes/no response to the question "Are you sick?").

While our results were not statistically significant, the misaligned group did display a later first meal time on non-school (9.5) versus school (8.7) days and a trend difference for the total meal period with a shorter duration between first and last meal on school days (577 minutes) compared to non-school days (589.2 minutes). These findings are in accordance with prior literature showing sleep timing and chronotype influence when eating occurs (C. M. Silva et al., 2016) and likely is perpetuating circadian misalignment in these students as suggested by findings that a delayed first meal disrupts peripheral clocks that signal back to the master clock (Shimizu et al., 2018) . The alterations in meal timing may act along the physiological path outlined above in the background to directly depress mood, as delayed meal offset may result in more TRP being used to create melatonin instead of 5-HT (Pereira et al., 2017). Further still, the melatonin that is produced is not active for as much time, as misaligned individuals also exhibit less total sleep time, which should feasibly decrease the effects of its inhibition of SERT (Matheus et al., 2010).

The results of this study show no predisposition to circadian misalignment based on demographics, which differs from prior studies (Marczyk Organek et al., 2015; Roane et al., 2014). As an important note, however, a study involving a larger Hispanic sample size may be necessary due to the fact that the current study showed a trend but did not have a large enough sample to test true statistical significance (N = 4).

While analysis showed that circadian misaligned students did have a significant difference in phase preference with a lower score indicating a tendency towards more evening type preference, individuals categorized as misaligned did not meet criteria as evening types on average. These findings suggest that circadian misaligned students, while not experiencing a strong evening type preference, do prefer a more evening type-like schedule (later bed and wake times) when compared to circadian aligned students. This type of circadian dysregulating behavior is common in adolescents and young adults (Crowley & Carskadon, 2010). The misaligned group also reported increased symptoms of sleep inertia on school days (feeling refreshed rating of 6.6) compared to non-school days (7.3). Furthermore, later bedtime and waketime predicted sleep inertia symptoms on both school and non-school days. These results suggest that misaligned students resemble individuals with DSPD, despite not technically meeting the formal requirements to be defined as evening type by the CS scale (Alvarez et al., 1992).

The similarity between misaligned students and DSPD patients is further strengthened by their reported sleep patterns. On school days, the two groups had a non-significant difference in bedtime (misaligned = 00:30, aligned = 00:00), but a significant difference in waketime (misaligned = 07:30, aligned = 06:54); whereas, on non-school days, a significant difference was present for both bedtime (misaligned = 00:48, aligned = 00:06) and waketime (misaligned = 08:06, aligned = 07:24). Consequently, total sleep time was shorter on school days for misaligned students (misaligned = 394.3 minutes, aligned = 412.2 minutes), but similar on non-school days (misaligned = 424.1 minutes, aligned = 411.2 minutes). As such, it was not unexpected that sleep efficiency, determined by the percent of sleep duration occurring during the sleep period, for the two groups was significantly different on school days (misaligned = 82.2%, aligned = 88.5%), but not on non-school days (misaligned = 83.7%, aligned = 85.8%). These findings suggest that misaligned students are attempting to adhere to social norms on school days, but are not filling their sleep period efficiently with sleep; however, on non-school days their sleep period is filled more efficiently with sleep when allowed to follow their internally preferred schedule.

Given the misaligned groups more delayed phase preference, their chronotype was likely contributing to their delayed sleep patterns (Vitale et al., 2015). Misaligned students reported wake times that were on average over 30 minutes later than aligned students for both school and non-school days. Thus, their later waketime likely meant their first light exposure is also delayed, which will perpetuate the misalignment between their internal circadian clock and societal timing. Since wake time was also one of the statistically significant predictors of lower mood ratings, findings provide support for the claim that misaligned individuals may be more prone to mood disturbance than aligned individuals.

Our findings did not reflect previous studies showing circadian misalignment contributed to decreased physical activity and disturbed immune functioning (Labrecque & Cermakian, 2015; Yamanaka, 2006); however, later bedtime on non-school night did show a trend in predicting decreased self-reported physical activity.

Strengths

The purpose of the current study was to examine an area that has not previously been well explored – impact of circadian misalignment, sleep patterns, and meal timing on mood and daytime functioning among medical students in the U.S. As such this study provides needed pilot findings that can inform future studies by raising awareness about problems found in a current gap of knowledge regarding sleep in medical students. The current study examined sleep behaviors leveraging a prospective study design that included sleep disorder measures as well as daily sleep records. The use of daily records enabled better reporting of sleep timing and meal pattern behaviors. Additionally, our sample consisted of students in a Doctor of Osteopathy program, which expanded the medical student literature.

Limitations

The conducted study utilized an archival data set and not a new data set designed specifically for the purposes of this study. However, the data set used was originally intended to ascertain sleep behaviors in medical students as well as health outcomes, and is therefore an acceptable source of data for the current study. The study data did not include biomarkers of circadian phase (melatonin) or mood (serum 5-HT); however, behavioral data reflecting these biomarkers was obtained (Baron & Reid, 2014; C. M. Silva et al., 2016; Vitale et al., 2015). Additionally, behavioral patterns were the primary concern of the current study in order to identify potential points of intervention to be examined in future studies. These findings may also be limited in generalizability due to the utilization of a sample of convenience. Given the intention was to procure preliminary data, the sample was justifiable. Finally, this study used self-reported data which may induce bias. Study design utilized standard methods of data collection supported the literature (Biddle, Robillard, Hermens, Hickie, & Glozier, 2015; Thurman et al., 2018).

Future Directions

These preliminary study results demonstrate a need to further study the effects of circadian misalignment in medical students. Of note is that 65% of the sample met study criteria for circadian misalignment indicating that this is a significant health concern in this population. Students who were circadian misaligned were more likely to engage in behaviors that promote continued circadian misalignment. Furthermore, negative health and wellness outcomes were associated with symptoms of chronic circadian misalignment. Many of these students are likely unaware that circadian misalignment is a major concern as circadian misaligned individuals typically do not realize the severity of their decreased function (Chellappa et al., 2018). Further compounding the issue is the fact that sleep as a topic of medicine is traditionally under-studied by medical students so they are not exposed to education on the topic to increase awareness (Rosen et al., 1993). This combination likely contributes to an increased burden on a significant portion of the medical student population. As such, one area of further research would be to explore the impact that sleep education within the medical curriculum has on medical student health behaviors. Further research in this area will be able to better inform the health and wellbeing of this important population and may reveal viable interventions in order to prevent adverse health outcomes among medical students around the world.

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