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Work Around the Clock: How work hours induce social jetlag and sleep deficiency

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Introduction

As much as our understanding of human health and disease is predicated on behaviors and exposures during wakefulness, several decades of research have begun to uncover the importance of sleep and its impacts on physiology and pathology. From an evolutionary perspective, sleep places humans in a state of vulnerability, and yet this behavior is shared universally by mammals.[1] However, we now understand that sleep duration and timing are essential for optimal cognitive and physiologic functioning.[2–4] Sleep and wakefulness are impacted by several external and internal factors, but none are more important than the endogenous circadian system.

The term circadian is derived from Latin meaning “about a day” and the circadian “clock” is an endogenous, self-sustaining, biological time-keeping system with a period of approximately 24 hours in humans.[5] This system is both extremely precise, with a standard deviation of 12 minutes within mice models and 8 minutes in humans, yet entrainable to external and behavioral stimuli known as ‘zeitgeibers’ (i.e. ‘time-givers’).[6,5,7] Mechanistically, the precision of the circadian clock is established by an autonomous, transcriptional auto-regulatory feedback loop that exists both centrally

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within the suprachiasmatic nucleus of the hypothalamus, as well as in peripheral tissues.[8, 9] The suprachiasmatic nucleus further supports the system's pliability by modulating the pineal gland's secretion of the hormone melatonin in response to changes in light-timing exposure.[7–10] In the laboratory, the circadian clock is measured via oscillations in physiological processes (i.e., core body temperature, cortisol, or melatonin concentrations).[11] Circadian "rhythms" are the physiological outputs of the circadian clock, such as the circadian-based variations in hormone secretion, enzyme activity, or organ function, among others.[12,11]

Much of what is known about the circadian clock and its impacts on physiology has come from studies in which the clock is desynchronized from confounding behaviors like sleep, wakefulness, eating and physical activity, as well as from external stimuli such as light, all of which having the potential to influence physiological rhythms. This desynchronization is also understood as *circadian misalignment*, a behavioral pattern in which sleep and activity occur during conflicting circadian phases (e.g., sleeping during the day, eating and activity during the night). Circadian misalignment can also be observed naturally in individuals experiencing irregular sleep either resulting from endogenous factors, such as sleep disorders, or from exogenous factors such as work and social schedules (Figure 1). We will review the fundamental relationships between the circadian timing system and biological processes, considering how common practices, such as shift work and variations in sleep timing on work/school versus work/school free days (i.e., social jetlag) disrupt circadian alignment and predispose individuals to cardiovascular, metabolic, and pulmonary disease.

Circadian Impacts on Physiology

The self-regulatory genes that define the circadian clock can themselves directly impact the transcription of genes involved in biologically relevant pathways. Research into mouse models have shown that nearly half of all transcripts in the genome are under circadian control.[13] This is true even within complex tissues such as the liver and heart, which both demonstrate circadian variations in gene expression, though the expression profile varies significantly between the two.[14] This variation in gene expression ultimately manifests in circadian dynamics of macroscopic physiology.

Cardiovascular System

Within the cardiovascular system, many processes are influenced by circadian timing. Under tightly-controlled in-laboratory environments, blood pressure displays circadian rhythmicity with a predictable zenith and nadir in the absence of sleep.[15] However, sleep further causes a "dip" in blood pressure in most healthy individuals.[16] While, in the heart, this is likely the result of cortisol and vagal modulation, variation in blood pressure can also be attributed to the influence of circadian timing in both the kidney–mediated by the Renin-Angiotensin-Aldosterone system–and via blood-flow dynamics within the vasculature.[17–19] Circadian timing, in addition to diurnal variation, may also play a role in cardiovascular dysfunction, as evidenced by the observed increase in major cardiovascular events during the morning.[20, 21] Several factors have been implicated in this epidemiological phenomena and evidence suggests that the circadian-based variation in cortisol–a stress hormone that is elevated during the morning and impacts cardiovascular and metabolic functioning–may play a role.[22] Thus, these factors place a pre-disposed heart at increased risk.

Metabolism

Many rate-limiting enzymes involved in metabolic pathways, such as in fatty acid and sterol biosynthesis, are under circadian control.[23, 24] Moreover, many metabolic hormones and subsequent metabolites demonstrate circadian rhythmicity.[25] Glucose homeostasis also appears to depend on circadian influences, with one study finding that ablation of circadian genes in the pancreas triggers poor glucose control and the onset of diabetes mellitus in mice.[26] In a seminal study investigating the impact of circadian timing on postprandial glucose, insulin, and cortisol, healthy participants were given iso-caloric meals every 6 or 12 hours over a 36 hour period, with both scenarios involving a "morning" (0600h) and "evening" (2000h) meal. Results showed that postprandial glucose response was greater following evening meals but, interestingly, was not associated with a commensurate increase in insulin secretion.[12] This latter finding suggests possible circadian variation in beta-cell function in the pancreas, i.e., variation in insulin production in response to increased blood glucose. The circadian variation in insulin sensitivity and beta-cell function, specifically as it relates to circadian misalignment, will be discussed later. The *Dawn Phenomena*, a symptom of diabetes in which an increased dosage of insulin in type 2 diabetics is required in the morning for what is believed to be the result of decreased insulin sensitivity, may also exemplify how circadian timing impacts physiology in the diseased state.[27]

The process of respiration displays circadian rhythmicity during controlled in-laboratory settings, with increased and decreased respiratory rates observed in the morning and evening, respectively.[28] Moreover, this variation observed in the laboratory persists even as the circadian clock is dissociated from behaviors such as sleep, wakefulness, eating and activity.[28, 29] The decrease in apparent respiratory drive at night is believed to play a major role in the pathophysiology of sleep disorders as well as contributing to increased rates of respiratory failure at night.[30] As seen with diabetes, chronic diseases like asthma are also affected by circadian timing. Most notably, it has long been observed that asthma symptoms increase at night, likely reflecting the injurious affects that circadian variation can have on predisposed individuals.[31–34]

Shift work and Social Jetlag

Sleep deficiency and dysregulation can result from several mechanisms involving endogenous and/or exogenous factors. We will consider how human behaviors, such as shift work and social jet lag (Figure 1), affect sleep behavior, induce circadian misalignment, and impact health.[35–38]

Shift Work

An estimated 17-20% of the US workforce engages is some form of shift work, which typically involves periods of work that occur during normal sleep time.[39] In this way shift work can precipitate circadian misalignment which manifests most directly in irregular sleep schedules, less overall sleep, and poorer sleep hygiene when compared to a daytime work schedule.[40] The American Academy of Sleep Medicine has developed the *Shift-Work Sleep Disorder* diagnosis in response to this robust finding of sleep deficiency among shift workers.[41] Contrary to what may be commonly believed, adjustment to night-shift work, as measured via melatonin phase, appears minimal even among chronic night-shift workers with one report finding that less than a quarter of these individuals demonstrate “substantial” circadian adjustment.[42, 43] Without the capacity to sufficiently shift the circadian clock, many shift workers are exposed to extended episodes of circadian misalignment, which is linked to a multitude of adverse health outcomes.[40, 43–48]

Regarding chronic disease, shift workers have up to a 40% increase risk of cardiovascular disease, a 25-45% increase risk in obesity, a 10-16% increased risk of diabetes, and up to a 55% increase in odds of having asthma.[44, 45, 47, 49] Given these epidemiological findings, recent work has been done in laboratory settings to understand how much of these adverse health trends can be explained by circadian misalignment versus other factors such as food intake, activity level, sleep and light exposure.

Cardiovascular System

In investigating the impacts of shift work on cardiovascular biomarkers, one study exposed chronic shift workers to two 3-day protocols, one of which simulated night work (12-hour inverted behavioral and environmental schedule) and the other simulated day work. Circadian misalignment, as represented by a simulated night shift, was significantly correlated with increased blood pressure and increased C-reactive protein, an inflammatory marker implicated in the progression of heart disease.[50, 51] Exposure to similar protocols have revealed that circadian misalignment significantly increases the serum concentration of other inflammatory markers, including IL-6 and TNFα, which are themselves risk factors for cardiovascular disease.[52] Other risk factors for disease have also been found to change with exposure to shift work. Blood pressure “dipping” (≥10% reduction in blood pressure as compared to daytime levels) during sleep is a typical phenomenon in healthy individuals, while “non-dippers” (<10% reduction in blood pressure as compared to daytime levels) have been found to have increased mortality and cardiovascular disease risk.[53, 54] A study investigating how shift work impacts “dipping” status found that among newly hired transit operators who began working the early-morning shift and who were considered “dippers” prior to employment, 62% were converted to a “non-dipper” status at 90 days of working early-morning shifts.[55] This is in comparison to those who began working the day shift, all of whom were found to have healthy blood pressure dipping at the 90-day mark; 50% of whom had converted to a dipping status during the study monitoring period.[55] Similar studies have been conducted to understand how shift work predisposes individuals to metabolic disease.

Metabolism

As stated earlier, shift work is associated with increased rates of obesity and metabolic disease.[46, 49, 56] To elucidate probable mechanisms, researchers using rodent models have shown that restricting feeding to only the rest phase—as is similar with night-shift workers who eat a significant portion of their calories during the circadian rest phase—results in significant increases in body weight, fat deposits and body mass index.[57, 58] This was true even though there was no statistical difference with control mice regarding total caloric intake and physical activity. Similar findings in human studies suggest that the mechanism of weight gain secondary to circadian misalignment is partly due to changes in energy expenditure that are not explained by variations in physical activity and caloric intake.[59] In one study, researchers used an 8-day crossover protocol in which participants were exposed to either 5-days of simulated night shifts or day shifts, which was then repeated later using the same 8-day protocol with the alternative simulated schedule (night vs day shift). The study found that diet-induced thermogenesis (DIT), which represents a major component of daily energy expenditure, was 44% lower following evening as compared to morning meals and was primarily explained by circadian influence rather than behavioral pattern.[60] Surprisingly, circadian misalignment did not significantly impact DIT in this study although a similar study using a 6-day protocol with 3-days of inverted sleep and wakefulness (circadian misalignment) found a 3-4% decrease in overall energy expenditure, with a 4% decrease in DIT following meals consumed later in the evening.[61] This research suggests that food intake during the evening hours (i.e., during the circadian rest-phase), is metabolized differently than during the circadian daytime. For shift workers, food intake at night is often a necessity, which, considering this research, may help explain the increased body weight seen in epidemiological studies.

Underlying these links between adverse changes in body composition and simulated shift work is the change observed in insulin sensitivity and glucose tolerance under circadian misalignment. In a direct experiment looking into the impacts of melatonin on glucose tolerance, participants given an oral dose of melatonin in either the evening or morning had subsequent impairment in glucose tolerance.[62] This is relevant as mealtimes for shift workers often coincide with episodes of increased melatonin (i.e., at night during the circadian rest phase). In a more thorough in-laboratory examination of shift work pattern and glucose control, participants in an extended circadian disruption study were subjected to 3 weeks of both sleep restriction and extended days (i.e., >24 hours).[63] The study found that there was an increase in fasting glucose and post-prandial glucose levels of 8% and 14%, respectively, with corresponding decreases in insulin levels of 12-27% compared to baseline.[63] The study also found that a 9-day recovery phase following misalignment restored insulin and glucose ranges to baseline levels in most participants, implying that the system is rectifiable.

Insulin dysfunction seen in circadian misalignment highlights the interplay between the function and/or reactivity of pancreatic beta cells and insulin sensitivity in peripheral tissues. In normal circadian alignment, beta-cell function is decreased during evening hours, resulting in decreased serum insulin relative to blood glucose levels.[12] This may explain why those who eat later tend to have poorer metabolic profiles.[35, 64, 65] However, the mechanism changes when the circadian system is misaligned.[64] In a study of chronic shift-workers exposed to a 12-hour inverted behavioral schedule to mimic shift work, researchers found misalignment to result in a 10% increase in late phase post-prandial insulin even while postprandial glucose remained elevated.[43] These results suggest that glucose tolerance diminishes secondarily to decreased insulin sensitivity in peripheral tissues. This may help explain the increased incidence in type 2 diabetes among shift-workers as this disease is partly defined by insulin insensitivity.[66]

Shift work is not the only behavioral pattern to impact sleep, circadian rhythms, and health. Social jetlag is a similar phenomenon with a less drastic effect on sleep patterns but with the potential to have equally deleterious health consequences.

Social Jetlag

Social jetlag is defined as a sleep pattern that varies between work/school days and free-days (Figure 2). During consecutive work or school days, individuals are likely unable to obtain sufficient sleep, or sleep at un-preferred times, and thus resort to “sleeping-in” on free-days to recover. Typically, sleep is increased by 2-3hours during this ‘weekend recovery’ sleep, which subsequently shifts the individual’s wakefulness schedule in a manner similar to travel-related jetlag.[67] Social jetlag is most common among late chronotypes–colloquially known as “night owls”–whose biological waking time is at odds with work hours.[68] Late chronotypes, in comparison to early chronotypes who fall asleep early and wake early, are more common and represent a growing demographic in industrialized nations due to societal-selection for prolonged social/work schedules with increased light exposure at night.[68, 69]

Poor health is more commonly observed in late chronotypes, who are 2.5 times more likely than early chronotypes to report their general health to be poor or fair.[70] Late chronotypes who are more likely to experience severe social jetlag are also more likely to smoke, participate in sleep-interfering behaviors, are less physically active and report increased rates of sleep disturbance.[71] Objectively speaking, late chronotypes have a 2.5 fold increase in type 2 diabetes mellitus, 1.2 fold increase in obesity, and more broadly a 1.3 fold increase in metabolic syndrome, the odds of which increasing by 30% for every additional hour of “oversleep” on free-days.[72, 73] Late chronotypes are also at increased risk of developing asthma.[72] In terms of cardiovascular health, late chronotypes have 1.3 fold increase in hypertension and those experiencing social jetlag have a 20% increased cardiovascular risk which also increases by 30% for each additional hour of “oversleep”.[72, 74] Some have linked increased cardiovascular-related deaths on Mondays to the impacts of social jetlag, though others cite a lack of sufficient evidence for the epidemiological phenomenon.[75, 76] Lab research into social jetlag has found similar underlying pathological processes to that of shift work. Regarding insulin sensitivity changes, a study using healthy participants found there to be a 20% reduction in early-morning oral and intravenous insulin sensitivity following 5-days of sleep restriction (5 hours per night), with the magnitude of insulin sensitivity directly correlated with the magnitude of circadian misalignment.[77] An investigation into the chronic impacts of social jetlag in mice found that shifting the 12-hour light exposure schedule by 6-hours every seven days resulted in decreased lifespan and survival rates.[38]

Though shift work is a more severe form of circadian misalignment, social jetlag is linked to a degree of misalignment sufficient to generate similar adverse trends in cardiovascular, metabolic and respiratory health. From a population health standpoint, social jetlag is more widely experienced in industrialized nations and its consequences more broadly felt, as in one study that found social jetlag induced by time zones to associate not only with poorer health trends, but also poorer economic performance.[78] The adverse impacts of social jetlag are not experienced exclusively by working adults. In fact, social jetlag appears to be an epidemic among adolescent populations. [79]

The physiologic changes occurring during adolescence, in conjunction with the psychosocial factors related to this phase of early life represents a "perfect storm" that predisposes this population to social jetlag.[79, 80] Melatonin release is delayed during adolescence in part due to normal physiological changes, but also due to increased light sensitivity.[81, 82] Furthermore, adolescence represents a phase of increased social responsibility and independence (i.e., sleep-time autonomy, academic scheduling and pressure, and increased screen time).[83] These factors place adolescents at increased risk of experiencing social jetlag, which is positively associating with anxiety symptoms, poorer eating habits, and body mass index percentile.[69, 83–85] However, sleep deprivation and social jetlag among adolescents can be mitigated by delaying school start times, though such singular measures come with their own socio-political hurdles.[86]

Countermeasures

The most salient physiological symptoms of shift work and social jetlag are sleep disruption and decreased alertness while awake. Symptom management has largely centered around the latter via the use of stimulants. Caffeine has for centuries been used to increase awareness and has been shown to improve psychomotor vigilance and wakefulness, particularly during times of circadian misalignment.[87, 88] Periodic naps, in conjunction with caffeine, have been found to further augment wakefulness, alertness and psychomotor vigilance testing on simulated night shifts.[87] However caffeine can diminish the quality of daytime sleep recovery, thus making the balance between increasing alertness and maintaining sleep quality difficult to achieve.[89] Modafinil, a psychostimulant used to treat excessive daytime sleepiness in patients with narcolepsy and obstructive sleep apnea, has been shown to decrease sleepiness in laboratory settings, as well as improve tests of memory and attention when compared to placebo.[90–92] However, there is no improvement in duration or quality of daytime recovery sleep, indicating that long-term use may likewise be less effective.[90] Though capable of improving performance measures during the short-term, stimulants diminish the duration and quality of recovery sleep, which is essential to restoring and/or adjusting the circadian clock while also being protective against disease. Therefore, approaches to improve sleep recovery have also been tested, including the use of melatonin which has been shown to improve sleep duration during daytime sleep.[93] However, there is minimal effect on performance measures assessed during subsequent evening shifts.[93]

Alternatively, changes in shift-scheduling and other environmental measures may help in diminishing the degree of circadian misalignment. Human circadian rhythms have been shown to respond more quickly to phase delay, (i.e., going to bed and waking up later), than phase advance, (i.e., going to bed and waking up earlier).[94] Thus, establishing shift schedules to rotate clockwise (day to afternoon, afternoon to night) and also to involve smaller magnitudes in transition (<6-hours) may mitigate misalignment.[94, 95] Controlling for other variables like light exposure–e.g. wearing sunglasses prior to day-recovery sleep, or "pulses" of bright light during work–, room temperature during sleep and work, as well as food intake can also improve overall perception of sleepiness and be protective against adverse health effects of shift work.[94, 96, 97]

For those working permanent night shifts, the goal is to allow for both alertness and productivity during the night shift, while also preserving some degree of daytime wakefulness to be utilized socially on free-days. Without a medicinal quick-fix, a “compromised” shift-schedule in the circadian clock has been proposed, (i.e., permanent shift in the circadian-phase positions).[98] By using bright light pulses during simulated shift work, dark sunglasses for use outside to block blue-enriched light, adherence to scheduled sleep times in dark rooms, and outdoor afternoon light exposures to mitigate extreme rhythm delay, researchers have been able to delay participants’ circadian clock to have a nadir in alertness at ~10:00.[99] In comparison to controls who had a circadian nadir of ~06:00, the treatment group was found to have increased overall sleep–sufficient sleep during daytime following night shifts and late nighttime on days off–, as well as improved performance during night shifts.” As with all attempts at circadian entrainment, the challenge with a compromised circadian-phase shift is adherence to the sleep-behavior regimen.

Summary

The circadian timing system is a powerful biological system that, when in sync with our daily habits, aids in optimal physiological functioning. However, when exposed to environments that induce misalignment, research demonstrates not only acute, but also long-term impacts on cardiovascular, metabolic, and respiratory health (Figure 3). This is not restricted to those working night shifts, as the adoption of prolonged work and social schedules, and increased light exposure at night have led many in industrialized countries to suffer from varying degrees of circadian misalignment. This social jetlag has also been shown to contribute to worsening health trends. Several modalities have been researched to address the symptoms of sleep deficiency induced by shift work and social jetlag, yet it seems conservative measures, most notably that of consistent sleep schedules in addition to proper sleep hygiene (light exposure, room temperatures, food intake), are the most protective and cost effective.

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Synopsis:

A growing body of evidence has placed an increasing emphasis on how sleep affects health. Not only does insufficient sleep make us subjectively feel worse, but is associated with chronic diseases that are considered epidemics in industrialized nations. This is in part due to the growing need for prolonged work and social schedules, exemplified by shift work, late-night weekends, and early morning work/school start-times (i.e., social jetlag). Here, we will consider fundamental relationships between the circadian clock and biological processes and discuss how common practices like shift work and social jetlag contribute to sleep disruption, circadian misalignment, and adverse health outcomes.

Clinics Care Points

- Assessment of sleep patterns, behaviors, and hygiene is an essential component of a thorough medical history.
- Understand that chronic diseases are significantly impacted by and often develop within a context of poor sleep hygiene, therefore sleep health should be addressed in care planning and disease management.
- Encourage proper sleep hygiene beyond the usual “try to sleep more”:
  - Establishing and adhering to consistent sleep schedule on work and off days.
  - Control light exposure leading up to and during sleep, i.e. no cellphones in bed.
  - Moderate use of stimulants.
  - Recovery days following periods of sleep deficiency are effective at rectifying the circadian system.
- Minimize large meals during evening periods when one is typically sleeping.
- Advocate for your patients with their employers, highlighting not just the health benefits of consistent work and sleep schedules, but also the improved productivity.
- Ensure you yourself practice proper sleep hygiene; before you can take care of others, you must take care of yourself.

Key Points:

- The endogenous circadian time-keeping system influences human physiology both in healthy and in diseased states.
- Misalignment between behaviors and the circadian clock (i.e., circadian misalignment) disrupts optimal functioning of physiologic processes, predisposing individuals to cardiovascular, metabolic, and respiratory disease.
- Working during biological nighttime hours (i.e., shift work) and weekly changes in sleep and subsequent circadian timing (i.e., social jetlag) are common causes of circadian misalignment and are associated with impaired health profiles.
- Countermeasures, such as improving sleep hygiene, maintaining consistent sleep schedules, and scheduling work timing to match endogenous circadian timing, have been shown to be effective in combating circadian misalignment.

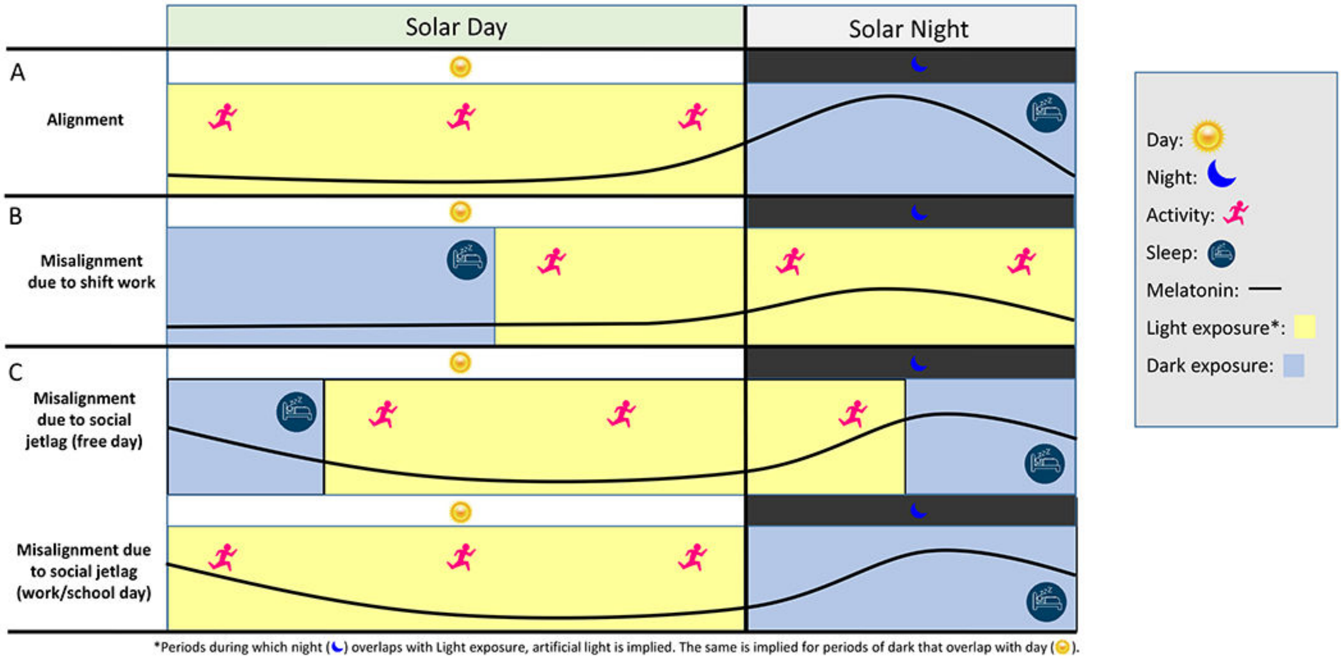

Figure 1. Relationships between light exposure, activity/rest patterns, and the melatonin rhythm during circadian alignment, shift work, and social jetlag.

The top row (A) displays an alignment in which activity/rest, the internal biological circadian day/night (represented by the circadian melatonin rhythm) and light exposure are synchronized, the middle row (B) demonstrates how work hours (i.e., shift work) create a misalignment by altering light exposure and activity patterns and dampens the melatonin peak at night, and the bottom row (C) represents misalignment caused from social jetlag on the weekend. Specifically, social jetlag is a phenomenon in which individuals shift bedtime later, and thereby are exposed to light later, on free days resulting in a free-day delay in the circadian clock (C, top row) which subsequently causes a misalignment when an individual must return to a work/school schedules (C, bottom row).

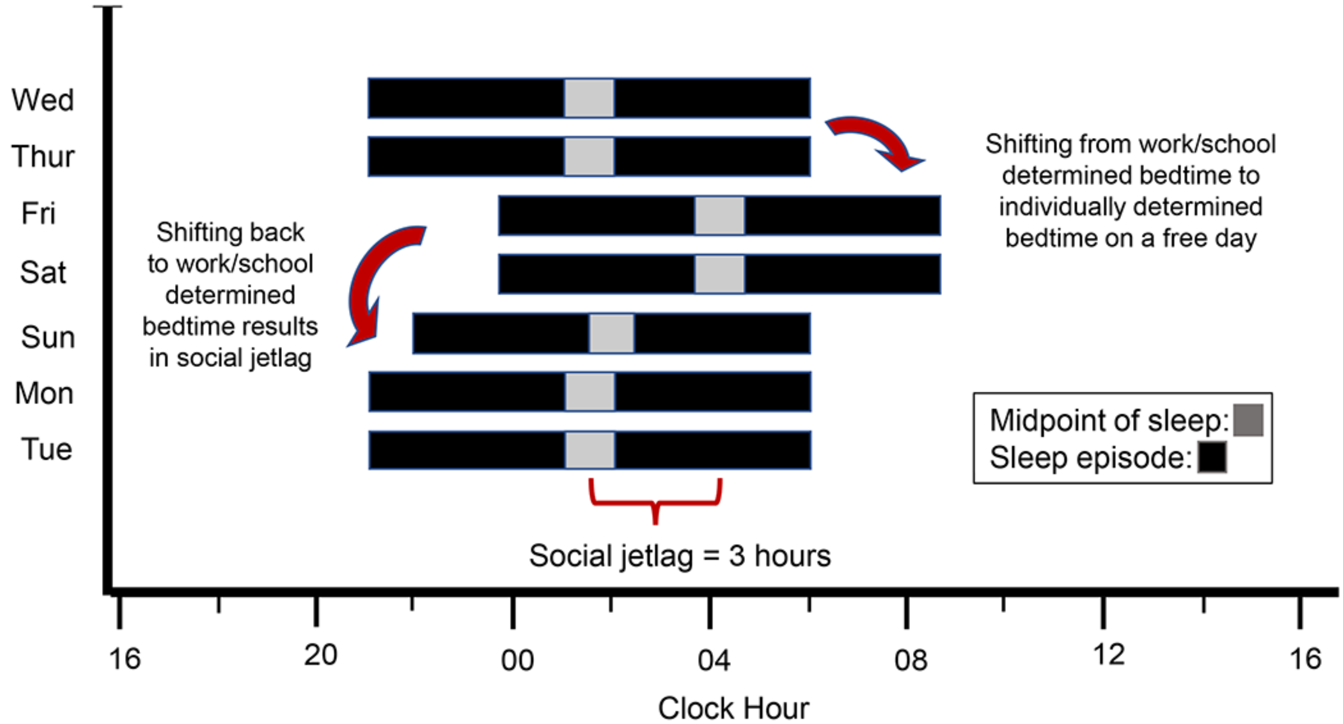

Figure 2. Example of a social jetlag schedule.

Delayed sleep onset on weekends due to individually preferred bedtimes results in later sleep and light exposure timing. Return to work/school-determined sleep pattern abruptly advances sleep timing in a way similar to air-travel associated jetlag.

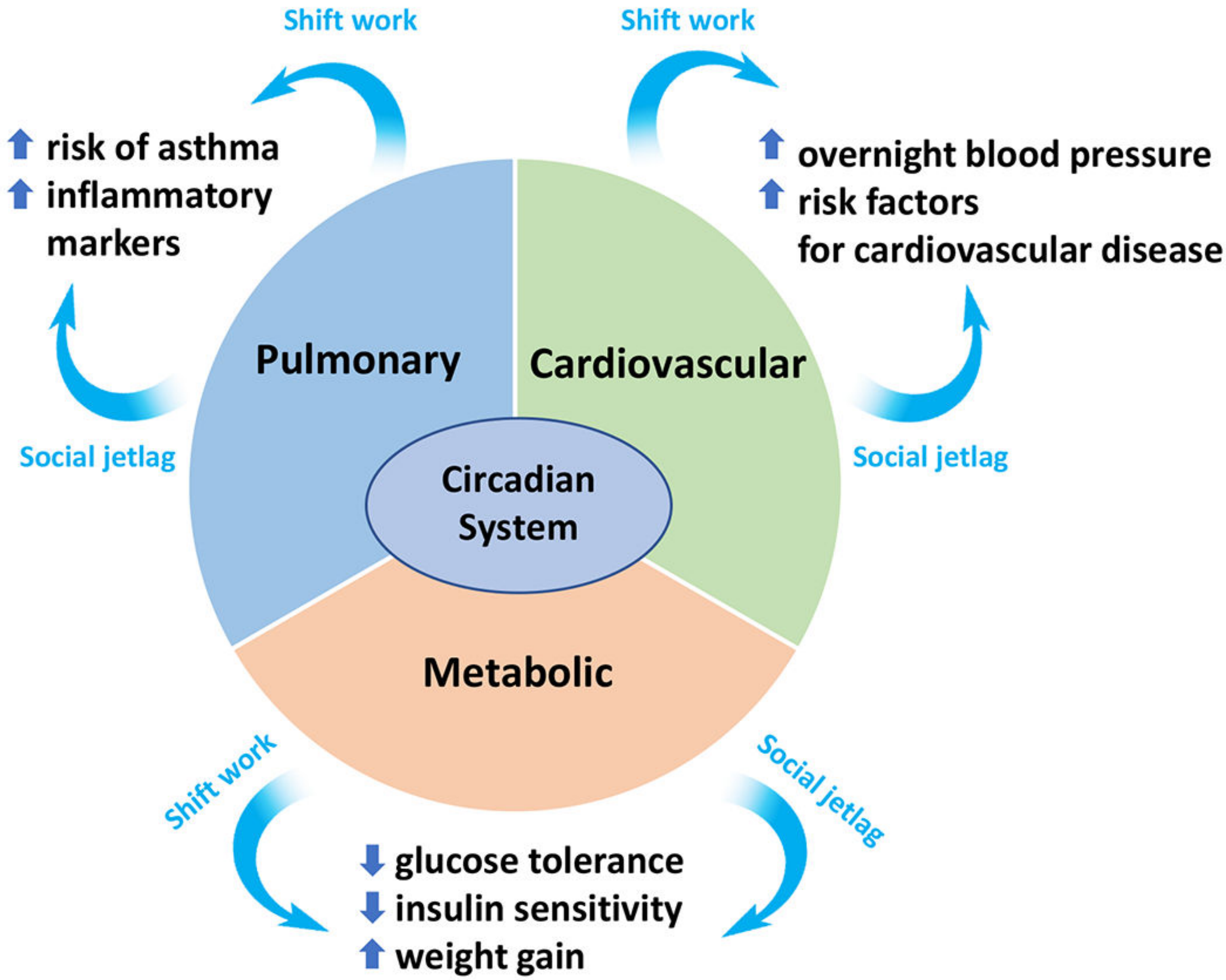

Figure 3. Cardiometabolic impacts when the circadian system is disrupted by social jetlag and shift work.

A typically well-functioning network between the circadian system and major physiological systems is disrupted by social jetlag and shift work, resulting in adverse health patterns that predispose to disease development and progression. Blue arrows point to examples of the disruptive sequelae of social jetlag and shift work.