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Shift Work: Disrupted Circadian Rhythms and Sleep—Implications for Health and Well-Being

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Abstract

Purpose of review—Our 24/7 society is dependent on shift work, despite mounting evidence for negative health outcomes from sleep displacement due to shift work. This paper reviews short- and long-term health consequences of sleep displacement and circadian misalignment due to shift work.

Recent findings—We focus on four broad health domains: metabolic health; risk of cancer; cardiovascular health; and mental health. Circadian misalignment affects these domains by inducing sleep deficiency, sympathovagal and hormonal imbalance, inflammation, impaired glucose metabolism, and dysregulated cell cycles. This leads to a range of medical conditions, including obesity, metabolic syndrome, type II diabetes, gastrointestinal dysfunction, compromised immune function, cardiovascular disease, excessive sleepiness, mood and social disorders, and increased cancer risk.

Summary—Interactions of biological disturbances with behavioral and societal factors shape the effects of shift work on health and well-being. Research is needed to better understand the underlying mechanisms and drive the development of countermeasures.

Keywords

Circadian Misalignment; Sleep Displacement; Metabolic Health; Cancer Risk; Heart Health; Mental Health

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Conflict of Interest

James Stephen, Kimberly Honn, Shobhan Gaddameedhi, and Hans Van Dongen each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

It has long been recognized that shift work has a negative impact on health and well-being. Historically this has been attributed to adverse effects of long work hours, nighttime light exposure, and psychosocial factors—effects that are still recognized as relevant for tolerance to shift work [1,2]. However, the health consequences of shift work should first be understood in terms of a fundamental misalignment between the circadian (i.e., near-24-hour) rhythm of the endogenous biological clock and the timing of the sleep/wake cycle [3]. While this paper is concerned primarily with the long-term health consequences of shift work, the implications of circadian misalignment between the biological clock and the sleep/wake cycle are perhaps best illustrated by how such misalignment increases the risk of workplace accidents and injuries.

In healthy, non-shift workers with normal sleep patterns, daytime wakefulness is driven by the biological clock, which produces circadian rhythmicity driving increased alertness during the daytime and decreased alertness during the nighttime [4,5]. This circadian process is counteracted by a homeostatic pressure for sleep, which builds across waking hours [6,7]. When working during daytime hours, these two processes function in concert and in synchrony with the environmental light/dark cycle to maintain alertness while awake and at work, while allowing for consolidated sleep during the night. Working nights or early morning shifts means that an individual must be awake when the circadian drive for alertness is low and asleep when it is high, in opposition to the natural biological rhythm. This leads to shortened and disrupted sleep, and excessive sleepiness while awake [8,9]. This in turn yields increased errors in the workplace, greater risk of accidents and injuries, and degraded health [10,11].

Society is increasingly dependent on around-the-clock operations that require shift work. Many industries and services rely on a continuous workforce, including manufacturing, energy production, transportation, healthcare, law enforcement, and the military. Based on data collected in the US in 2004 (the last time such data were comprehensively collected), the protective services (police, fire, correction services) have the highest percentage of night and rotating shift workers of any occupation (24.8%), followed by healthcare providers (10.9%) [12]. Such workers, when assigned night shifts, early morning shifts or rotating shifts, must modify their sleep schedules from the normal nighttime hours, placing the individuals into a condition of circadian misalignment. In 2004, out of more than 15 million US employees working full time on shift or irregular schedules, 5.7 million worked schedules requiring work hours that displace sleep and force wakefulness to be misaligned with the natural circadian rhythm [12]. Given this relatively high prevalence, it is important to understand the impact of circadian misalignment resulting from shift work on workers' health.

In this paper, we review short- and long-term biological effects associated with displacing the sleep/wake cycle. We also discuss the role of psychosocial factors in the expression of these effects and their impact on health and well-being. There is a wide range of medical conditions potentially caused or influenced by shift work, and an exhaustive overview of the literature in this area is beyond the scope of the paper. Rather, we focus on four broad health

domains that illustrate important components of the health consequences of shift work: metabolic health, risk of cancer, heart health, and mental health, as illustrated in Figure 1.

Metabolic Health

Sleep displacement and altered meal timing due to shift work disturb hormonal balance—including key regulators of satiety and hunger, the hormones leptin and ghrelin, respectively [13]. Leptin reduces appetite and signals for the cessation of food intake. In addition to showing transient increases after meals, leptin levels display a circadian rhythm driven by the biological clock [13]. Ghrelin is a short-acting hormone that stimulates appetite. Ghrelin levels decrease after meals and normally display a reverse diurnal pattern from leptin [14]. Ghrelin levels are related to time fasting (i.e., time between meals) and have a central role in mediating food-seeking behavior and motivation, food intake, and body weight [15,16,17].

Under normal circumstances, ghrelin and leptin work in concert to regulate feeding behavior with appropriate meal timing, size, and nutrients. However, in shift workers, meal times must be altered in accordance with the displaced sleep/wake schedule, which disrupts the coordination between leptin and ghrelin and dysregulates downstream biological systems related to diet, weight, and metabolism. Laboratory studies focused on the immediate effects of circadian misalignment have demonstrated decreased leptin levels [13,18] and blunted post-meal suppression of ghrelin [19]. If findings from laboratory sleep restriction studies generalize to shift work, then this may be expected to promote weight gain through enhanced appetite for calorie-dense foods with high carbohydrate content [20], consumption of food at night, and increased caloric intake overall [21]. Indeed, night shift workers tend to have significantly higher body mass index (BMI) and greater waist-to-hip ratio than day shift workers [22,23,24].

Sleep displacement and altered meal timing due to shift work also disturb glucose metabolism [25], through mechanisms that have yet to be elucidated. In mice, chronic advances of meal time appear to induce insulin resistance, while chronic delays appear to elevate blood glucose levels [26]. In humans, presumably as a long-term consequence of altered glucose metabolism, shift work is associated with increased risk of type II diabetes [27,28]. Deteriorating glycemic control and glucose intolerance are also associated with shift work [29,30,31]. For long-term shift workers (>10 years), the increased risk of diabetes persists into retirement [28]. Exacerbating this problem is that night shift workers tend to crave calorie-dense foods with high carbohydrate content while on shift [32]. All-night fast food restaurants, vending machines, and institutional dining facilities cater to this by serving predominantly processed and fried foods. The increased diabetes risk may be further amplified by unhealthy changes in lifestyle associated with shift work (e.g., smoking, alcohol consumption, and lack of exercise) [33].

Metabolic syndrome and diabetes risk may be further increased by the timing of eating and food digestion being out of sync with peripheral oscillators in the liver [34] and gut [35]. Over the long run, physiological maladaptation to eating at abnormal circadian times is associated with developing metabolic syndrome (MetS) [36,37,38]. Working at night has been estimated to increase the risk of developing MetS by more than 50% [37]. Although

moderators such as diet, exercise, and body weight are important, the evidence of a general connection between shift work and poor metabolic health is strong.

There is some emerging evidence that long-term exposure to sleep displacement alters the composition of the gut microbiota (i.e., the bacteria in the gastrointestinal tract) [39]. Recent work indicates that the gut microbiome shows diurnal variations that are influenced by meal times and disturbed by circadian misalignment [40]. The gut microbiome both responds and contributes to host energy balance, and disruption is associated with inflammation, insulin resistance, and adiposity [41]. Disrupted rhythmicity in the gut microbiome may be involved in an immediate and frequently reported, yet hitherto poorly understood, effect of shift work, namely, gastrointestinal discomfort [42,43]. Dysfunction of the gastrointestinal tract may also explain the significantly higher rate of ulcers in night workers compared to day workers [44], and may have impactful consequences for shift workers' long-term health.

Cancer

The master circadian pacemaker, orchestrating rhythmicity throughout the body, is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Peripheral systems, organs, and cells also have their own circadian rhythms, a phenomenon commonly referred to as peripheral oscillators [45]. These peripheral oscillators are normally in sync with the master clock in the SCN, but altered sleep/wake schedules associated with shift work may desynchronize them [46].

Maintaining synchronized circadian rhythms in peripheral systems is critical for the fine-tuning of cellular processes including cell cycles, DNA repair, apoptosis (i.e., controlled cell death), and immune modulation [47]. Circadian misalignment may alter the rhythms of cellular circadian clocks, and it is believed that this may increase the risk of cancer [48]. Findings in animal models with environmentally disturbed circadian systems (simulated shift work) indicate that circadian disruption increases the progression of cancer, possibly through dysregulation of the cell cycle, accumulation of DNA damage, and reduced tumor suppression [49,50,51,52].

Another factor possibly involved in the link between circadian misalignment and cancer risk is the hormone melatonin. This hormone is produced by the pineal gland and normally secreted at night, with the timing of secretion regulated by the master circadian pacemaker in the SCN [53]. Circulating melatonin levels can be disrupted by circadian misalignment, as well as by nocturnal exposure to light—bright light has a direct (i.e., non-circadian) suppressing effect on melatonin secretion [54,55]. Importantly, melatonin is protective against oxidative DNA damage [56]. Thus, when melatonin is suppressed, naturally occurring DNA damage may accumulate faster than it can be repaired, which may contribute to the increased risk of cancer that has been observed among shift workers [57].

Based on information from animal models and epidemiological evidence from the shift-working population, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) has classified night shift work as a probable carcinogen, while acknowledging that there is currently limited evidence from human studies [58]. Indeed,

research findings regarding shift work and cancer have been mixed. That said, many studies have reported an association between shift work exposure and increased risk of breast cancer [59,60]. Night shift work has also been found to increase the risk of other cancers, including lung, colon, bladder, prostate, rectal, and pancreatic cancer as well as non-Hodgkin's lymphoma [61,62,63]. However, a number of studies have found no association between cancer and shift work [64,65,66,67]. The variability in these findings may be related to other contributing factors, such as individual differences in susceptibility to carcinogenesis, occupational exposure to carcinogenic agents, and lifestyle [68,69]. Taken together, the literature suggests that further studies are needed to quantify and understand the relationship between shift work and risk of cancer.

Heart Health

The master circadian pacemaker in the SCN of the hypothalamus is centrally located at the nexus of a number of neuroendocrine systems, one of which is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis produces a number of neurotransmitters and hormones, such as epinephrine (adrenalin) and norepinephrine (noradrenalin) as well as cortisol, with widespread effects across a range of biological systems. The production of epinephrine and norepinephrine influences the interaction between the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), which is referred to as sympathovagal balance.

Circadian misalignment causes internal desynchronization of the HPA axis [70,71]. Sympathovagal balance is then disrupted [72], as indicated by changes in heart rate variability that are believed to reflect increased risk of cardiovascular disease (CVD) [73]. The SNS is most active in times of heightened physiological arousal, and is often referred to as the "fight or flight" system. The PNS is most active in times of reduced physiological arousal, and is sometimes referred to as the "rest and digest" system. The dysregulation of these systems can have immediate and fatal consequences, such as sudden cardiac arrest. In law enforcement, approximately 7% of line of duty deaths are due to a fatal heart attack [74]. These deaths overwhelmingly occur when officers stress the sympathovagal system during times of desynchronization, such as during nighttime physical confrontations [75].

Working night shifts and rotating shifts has been associated with elevated risk of heart disease [76] and ischemic stroke [77,78]. Working nights also raises the prevalence of metabolic risk factors associated with these conditions [79]. However, adverse heart health outcomes seem to be tied not only to shift work and circadian misalignment, but also the presence of psychological and psychosocial stressors [80,81]. Chronic stress associated with shift work has been associated with an increased risk for coronary heart disease in both blue- and white-collar workers [82]. Changes in lifestyle habits associated with shift work do not appear to account for the elevated risk of coronary heart disease in these populations [83]. Despite the established link between circadian misalignment and hormone regulation related to heart health, the specific mechanisms connecting shift work and CVD remain elusive.

Candidate mechanisms underlying elevated risk for CVD due to shift work include disrupted 24-hour rhythms of blood pressure [84] and vascular function [85], atherosclerosis [86],

proinflammatory states [87], and altered lipid and glucose metabolism [88]. Shift work-related metabolic dysfunction and the various health consequences thereof, including obesity, metabolic syndrome, and type II diabetes (discussed above), also potentiate the development of CVD [88,89]. Adipokines (cell signaling proteins) secreted by fat tissue and involved in immune responses—and more generally the development of a compromised immune system due to circadian misalignment—may connect these different factors [90]. Further research into candidate mechanisms must consider not only circadian misalignment from shift work, but also socioeconomic indicators and occupational factors (e.g., physical/mental workload, workplace stressors) known to be associated with poor heart health [91].

Mental Health

As described above, circadian misalignment disrupts the internal synchronization of the HPA axis. Persistent stimulation of the HPA axis by external stressors in the face of circadian misalignment may lead to erosion of mental health in shift workers. Stimulation of the (desynchronized) HPA axis activates the fear system and blunts the reward system, leading to abnormal responses to stress [92]. As such, shift workers exposed to stressors at night may experience difficulty managing physiological and mental responses to these stressors.

The HPA axis hormone cortisol, which is central to the body's responses to stressors [93], has been used in many studies as an index of responsivity to stressors. Cortisol levels normally exhibit a pronounced circadian rhythm with a peak in the morning hours. Night shift work has been found to shift the timing of the cortisol rhythm [94], and rotating shift work has been reported to dampen the rhythms' amplitude [95]. Although it is unclear whether disruption of cortisol rhythms is causally involved, it is generally believed that shift work leads to heightened stress reactivity and—in those who are especially susceptible—the development of insomnia and shift work disorder [96]. In fact, the impact of altered stressor responses on the quality of sleep may be a critical mediator of emotion regulation [97], resilience to stress [98], and ultimately tolerance for shift work [1]. As many as 20% of shift workers ultimately opt out of shift work due to sleep disturbances and adverse stress reactions [82].

Although every occupation has the potential to be stressful, the protective services and healthcare occupations are inherently so [99,100]. These two occupational families also have a large proportion of staff working nights and rotating shifts. In addition to normal workplace stressors, the protective services and healthcare workers are often exposed to dangerous and traumatic events. Moreover, shift work can reduce contact with psychosocial factors that protect against stress. For example, shift schedules tend to limit social interactions—thus reducing social support [101]—and diminish sex life satisfaction [102]. Such work–life interference, whether perceived or real, has been found to be one of the most significant indicators of marital dissatisfaction for both shift workers and their partners [103].

HPA axis desynchrony due to circadian misalignment, increased exposure to stressors during night work, and reduced access to protective psychosocial factors lead to an increase in long-

term adverse health outcomes. For example, law enforcement professionals have a significantly higher risk of suicide and stress-related and mood disorders [104] than the general public. More research is needed to understand the mechanisms that underlie the interaction between chronic exposure to circadian misalignment and workplace stressors and the development of mental health disorders.

Conclusion

The empirical evidence suggests that circadian misalignment is associated with a range of short- and long-term, negative health outcomes related to metabolic and gastrointestinal health, cancer, heart health, and mental health (see Figure 1). However, these associations are complex and nuanced, with many mediating and moderating factors. When considering the impact of shift work on health and well-being, it is essential to also consider the effects of behavioral, societal and environmental forces that may ameliorate or exacerbate the biological consequences of circadian misalignment.

The potential for workers to self-select out of shift work causes a systematic confound in population health research known as the “healthy worker effect” [105]. Shift workers experiencing degraded health or well-being may transfer to the day-working population, leaving the shift work cohort relatively healthier and the day work cohort relatively less so. Complicating matters further, many of the effects of shift work on health develop gradually over time, and may not manifest until workers have ceased to work shifts [106]. This is particularly common in occupations that assign shift types based on seniority, where the more junior (typically younger and healthier) individuals work the shifts most likely to displace sleep. The overarching implication is that the health consequences of shift work may be greater yet than what the available literature would already suggest at face value.

Despite mounting evidence for negative health effects, a significant portion of the population continues to be willing to engage in shift work. Workers may have a variety of reasons for dealing with the physiological and psychological consequences of shift work in their chosen occupation, including financial considerations, child care arrangements, or personal preference [12]. Some occupations have high barriers for entry (e.g., educational achievement, vocational training, psychological or background screening) and form the source of an individual’s identity (e.g., nurses, police officers, soldiers). These occupations may retain shift workers that are not well adapted to circadian misalignment because the financial, social, and psychological capital invested to enter the occupation may outweigh the negative aspects of shift work.

Shift work-induced circadian misalignment not only affects sleep and health, it also determines when people can exercise, eat, socialize, and have sex—all factors that support physical and mental health. Workers typically learn through experience the importance of getting to sleep as soon as possible at the end of a night shift in order to optimize sleep duration, while they may not explicitly understand the underlying circadian and homeostatic processes of sleep regulation. This results in competition between the need for sleep and other demands, such as exercise, healthy eating, and personal care. These latter activities are then often done quickly or to a lesser standard (e.g., fast food), or foregone altogether,

making it difficult for shift workers to maintain a healthy lifestyle [107]. To illustrate this point, health promotion efforts focusing on healthy eating habits for shift workers are available [108,109]. However, actually making healthier meal choices—at odds with the night shift-induced cravings and the limited availability of healthy food options at night—is not only time-consuming but tends to be more expensive as well. Increased sleepiness and worsened mood associated with night work make it even more difficult to maintain a healthy lifestyle, and are a further impediment to change.

There is an urgent need for research to better understand the mechanisms that underlie the interactions between sleep displacement and circadian misalignment on the one hand, and behavioral and societal factors on the other hand, in shaping adverse health outcomes for shift workers. Such research is going to be critical to drive the development of effective countermeasures, without which workers—and ultimately society—continue to bear the cost of shift work-related health problems.

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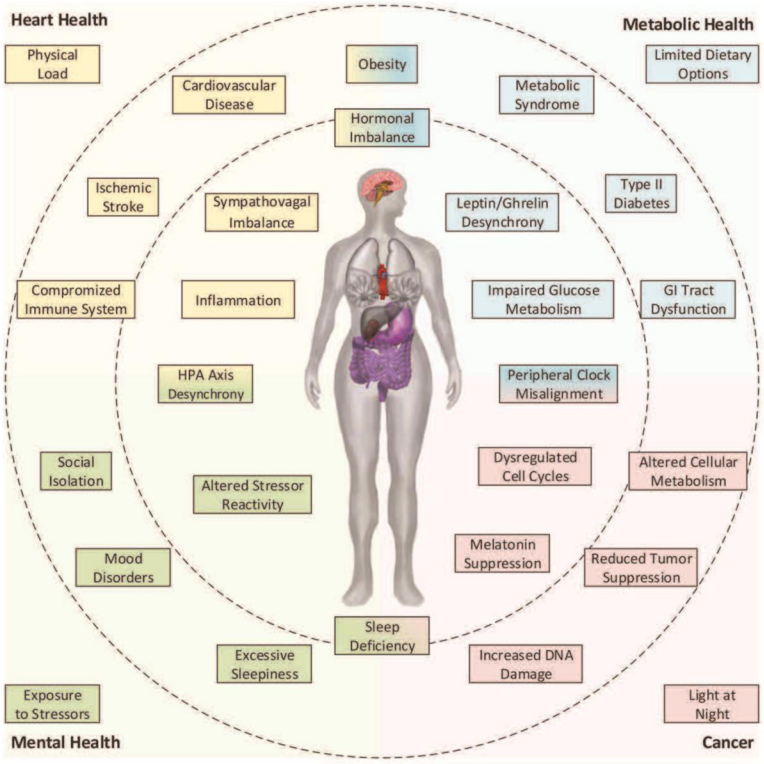

Figure 1.

Human pathophysiology due to shift work. In this paper, we discuss four broad components of health that are adversely affected by circadian misalignment due to shift work: heart health (top left quadrant), metabolic health (top right quadrant), cancer risk (bottom right quadrant), and mental health (bottom left quadrant). The inner circle represents biological systems that are disturbed by circadian misalignment, and the outer area represents broad psychosocial factors that interact with these disturbed biological systems. The ring between them illustrates key medical conditions that may arise from the interaction, for which shift workers are at elevated risk.