Metabolic and cardiovascular consequences of shift work: the role of circadian disruption and sleep disturbances

Running title: Metabolic and cardiovascular impacts of shift work

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Key words: circadian rhythms; sleep disturbances; atypical work schedules; diabetes; cardiovascular disease; metabolism

Abstract

Shift work, defined as work occurring outside typical daytime working hours, is associated with an increased risk of various non-communicable diseases, including diabetes and cardiovascular disease. Disruption of the internal circadian timing system and concomitant sleep disturbances are thought to play a critical role in the development of these health problems. Indeed, controlled laboratory studies have shown that short-term circadian misalignment and sleep restriction independently impair physiological processes, including insulin sensitivity, energy expenditure, immune function, blood pressure and cardiac modulation by the autonomous nervous system. If allowed to persist, these acute effects may lead to the development of cardiometabolic diseases in the long term. Here, we discuss the evidence for the contributions of circadian disruption and associated sleep disturbances to the risk of metabolic and cardiovascular health problems in shift workers. Improving the understanding of the physiological mechanisms affected by circadian misalignment and sleep disturbance will contribute to the development and implementation of strategies that prevent or mitigate the cardiometabolic impact of shift work.

Introduction

Cardiovascular diseases and metabolic disorders, such as type 2 diabetes, are major health problems and leading causes of death worldwide (World Health Organization, 2011). These non-communicable diseases share many modifiable risk factors, with tobacco use, unhealthy diets, limited physical activity, and harmful use of alcohol identified as the four main contributors (World Health Organization, 2011). However, mounting evidence suggests that shift work forms another risk factor for these health problems (Kecklund & Axelsson, 2016).

Although a uniform definition is lacking, shift work is commonly regarded as work that occurs outside regular daytime hours. Required for the round-the-clock operation of many services and industries, shift work is highly prevalent. Reports from Europe and North America have indicated that around 20-30% of the workforce describes their working schedule as different from a regular day shift (Williams, 2008; Alterman *et al.*, 2013; Eurofound, 2015), indicating that a substantial proportion of the working population is involved in shift work and is potentially at increased risk of developing a variety of health problems.

A multitude of factors associated with shift work may contribute to these increased health risks. However, it is becoming increasingly clear that circadian disturbances concomitant with this type of work schedules play a critical role (Nedeltcheva & Scheer, 2014; Reutrakul & Knutson, 2015). A better understanding of the health risks and the physiological mechanisms underlying circadian disruption is required for the development of strategies to prevent and counteract the health issues associated with shift work.

Therefore, the goal of this review is to discuss the evidence for the contributions of circadian and sleep disturbances to the development of metabolic and cardiovascular health problems in shift workers. We will first provide a brief overview of the circadian system and the two-process regulation of sleep and discuss the evidence of circadian and sleep disturbances in shift workers. Subsequently, we will describe the current understanding of the metabolic and cardiovascular effects of these two processes and discuss how these may lead to the physiological alterations that have been observed in shift workers. Lastly, we will review the epidemiological evidence for an increased risk of metabolic and cardiovascular diseases in chronic shift workers, highlight the limitations of the current body of research, and provide suggestions for future research.

The circadian timing system and the regulation of sleep

The circadian system allows organisms to proactively adapt their behaviour and physiology to the predictable daily variations of light and temperature caused by the Earth's rotation around its axis. At the molecular level, the circadian system consists of transcriptional-translational feedback loops that are present in nearly all cell types and persist even in constant environmental conditions (Takahashi, 2017). In short, a dimer consisting of CLOCK and BMAL1 proteins activates the transcription of *PER* and *CRY* genes. After translation, PER and CRY proteins dimerize, translocate to the nucleus, and suppress the activity of CLOCK and BMAL1, thereby inhibiting their own transcription. PER and CRY proteins are subsequently degraded and, as a consequence of their declining levels, the CLOCK:BMAL1 dimer can resume its transcriptional activity, closing the feedback loop. A variety of auxiliary core clock components and post-

translational modifications add to the robustness of this mechanism, creating a molecular feedback loop that sustains a rhythm with a period of approximately 24 hours (Takahashi, 2017). In addition, these core clock components regulate the expression of many downstream clock-controlled genes, giving rise to near 24-hour rhythms in a substantial proportion of the human transcriptome and proteome in various tissues (Loboda *et al.*, 2009; Akashi *et al.*, 2010; Li *et al.*, 2013; Moller-Levet *et al.*, 2013; Archer *et al.*, 2014; Arnardottir *et al.*, 2014; Chen *et al.*, 2016; Anafi *et al.*, 2017; Lim *et al.*, 2017; Depner *et al.*, 2018; Kervezee *et al.*, 2018). As a result, clock-controlled genes are involved in the regulation of diverse cellular processes, including metabolism and transcriptional regulation (Laing *et al.*, 2015). Under 24-hour light-dark cycles, clocks in peripheral tissues are entrained to the external environment by the central pacemaker in the suprachiasmatic nuclei (SCN) of the hypothalamus. This cluster of ~10,000 neurons receives photic input from the retina via the retinohypothalamic tract and transmits this information to peripheral tissues by controlling a variety of outputs, which include hormonal, neuronal, behavioural, and temperature signals (Dibner *et al.*, 2010).

The sleep-wake cycle is a distinctive pattern of behaviour whose regulation may be described by two physiological processes operating in concert (Borbély, 1982); namely, a circadian process operated by the SCN which regulates the propensity for sleep and wake across the day, and a homeostatic process which attempts to maintain a sleep-wake equilibrium (i.e., reduce variations from an individual's sleep requirements) by decreasing or increasing a drive for sleep based on preceding sleep-wake durations. The circadian regulation of sleep is facilitated by the rhythmic production and secretion of melatonin, which creates "windows of opportunity" for sleep during the night by

attenuating the alerting effect of the SCN (Lavie, 1997; Shochat *et al.*, 1997). Concurrently, the sleep homeostat helps individuals meet their sleep requirements by progressively increasing the physiological drive for sleep during periods of wakefulness and exponentially reducing this drive as their need is satiated. While the precise neurochemical basis of sleep homeostasis is still unclear, evidence exists that the physiological drive to sleep is associated with the accumulation and dissipation of adenosine during respective periods of prolonged wakefulness and sleep (Basheer *et al.*, 2000; Huang *et al.*, 2011; Roehrs *et al.*, 2011). Adenosine is proposed to have this soporific effect by inhibiting the activity of orexin neurons in the lateral hypothalamus which are essential for maintaining arousal during wakefulness (Liu & Gao, 2007; Sakurai, 2007; Huang *et al.*, 2011).

Circadian misalignment and sleep disruption in shift workers

Shift work inevitably leads to the displacement of light-dark, rest-activity, sleep-wake and fasting-feeding cycles, increasing the likelihood of circadian misalignment. This outcome describes an incongruent physiological state in which endogenous circadian rhythms, including the variation in sleep-wake propensity, are adapted to a day-oriented schedule, while demands posed by the external environment have shifted.

Various methods of determining circadian phase are used by researchers to tease apart the relative contributions of circadian misalignment, sleep disturbance, and other factors such as altered physical activity and food intake to the negative health effects associated with shift work. Currently, the phase of the central circadian clock (i.e. the timing of the

internal circadian system relative to external time) is typically determined by the measurement of markers such as melatonin in plasma or saliva, or its metabolite, 6-sulfatoxy-melatonin in urine (Mirick & Davis, 2008). The secretion of melatonin by the pineal gland is controlled by neural pathways emanating from **the** SCN and, in addition to regulating the timing of sleep, serves to synchronize peripheral tissues with the central clock in the SCN (Pandi-Perumal *et al.*, 2007). During regular nocturnal sleep and daytime activity, its levels in biofluids exhibit strong circadian variation with high levels during the biological night and low levels during the biological day (Figure 1) (Pandi-Perumal *et al.*, 2007).

The change in circadian phase during a period of night shifts has been addressed in various studies in permanent or rotating night shift workers to get an indication of the extent of circadian adaptation to different work schedules. One review of the available literature in permanent night shift workers concluded that 3% of workers show "complete adjustment" to their nightly working schedule**,** defined as (1) low melatonin levels during the work period and (2) the peak of melatonin occurring 2-3 hours after the onset of the daytime sleep period (Folkard, 2008). In comparison, 21% of workers show "substantial adjustment", meeting one of the two criteria for complete adjustment (Folkard, 2008). However, in a study involving police officers on rotating shift schedules, a larger proportion of the study population showed circadian adaptation: after one week of night shifts, the peak melatonin levels of 41% of the police officers occurred during their daytime sleep period (Boudreau *et al.*, 2013). Recently, in a study of 25 healthcare workers, no participants evinced substantial adjustment after 3-4 consecutive night shifts but there was substantial adjustment for 2 of the 4 (50%) participants who completed 6-7

consecutive night shifts (Stone *et al.*, 2018). This study also found that light-dark exposure contributed to 47% of the individual variability in phase response to night work. Thus, the discrepancies between the estimates in these studies may be due to the different criteria used to determine circadian adaptation as well as the study population (e.g. permanent night shift work versus rotating night shift work), roster organisation (e.g. number of consecutive shifts worked), and environmental conditions (e.g., light exposure).

Despite the wide range of estimates, it seems clear that the majority of night shift workers experience at least some degree of circadian misalignment (Figure 1). It should be noted that the assessment of circadian phase by melatonin, or other phase markers such as core body temperature or cortisol, requires the collection of multiple samples over a period of hours to days, ideally in controlled laboratory conditions to prevent the masking effects of light, activity, and/or stress (Mullington *et al.*, 2016). As a consequence, the studies investigating the degree of circadian adaptation in shift workers have been limited to small sample sizes. Given the potential adverse effects of circadian misalignment, as discussed below, there is a need for the development of biomarkers that can be readily applied on a large scale in field conditions to get a more reliable estimate of the extent of circadian adaptation in shift workers and to determine the rate of adaptation over time. Recent years have seen the development of various multivariate statistical algorithms to predict circadian phase from a single biological sample by employing transcriptomic data (Hughey *et al.*, 2016; Hughey, 2017; Laing *et al.*, 2017; Braun *et al.*, 2018; Wittenbrink *et al.*, 2018). While most of these methods have so far only been applied to data collected in controlled laboratory conditions, Wittenbrink et al. (2018) recently broke new ground

by developing a cost- and time-efficient assay to determine circadian phase from a single blood sample with unprecedented accuracy and precision, validating it in a wide range of chronotypes under naturalistic conditions. Nevertheless, these findings remain to be extended to more diverse groups of people, including shift workers, elderly, racial and/or ethnic minorities, and patient populations. In addition to a biomarker of circadian phase, it would be of interest to develop a biomarker of circadian disruption that is independent of time of day, in order to address the effect of circadian disruption on health and disease in population-wide studies.

The displacement of sleep-wake cycles is a prominent example of circadian misalignment caused by shift work, as shift workers' schedules can shift sleep opportunities to times that are inconsistent with their biological preferences, especially in the case of night work (Philip & Åkerstedt, 2006; Gander *et al.*, 2008). Consequently, shift workers often experience sleep loss, disruption, and displacement (Akerstedt, 2003; Roach *et al.*, 2003; Gander *et al.*, 2008; Ferguson *et al.*, 2010; Roach *et al.*, 2012). Indeed, while up to 10% of workers in Western nations report sleeping < 6 hours per night (Bin *et al.*, 2013), the prevalence of short sleep is greater amongst shift working populations (Sallinen & Kecklund, 2010). Approximately 30% of workers in industries that use non-standard work schedules and long work-weeks report sleeping ≤ 6 hours on average per night; this is more than the 24% of workers who reported this lack of sleep two decades ago (Luckhaupt *et al.*, 2010). Numerous studies comparing sleep duration across shift types have shown that workers on permanent days shifts sleep longer than those on permanent night shifts (Pilcher *et al.*, 2000; Akerstedt, 2003). Some evidence exists that shift workers on a permanent night schedule sleep more following a night shift than workers

on a rapidly rotating schedule. However, other studies suggest these differences are small and the literature indicates rotating workers may make up for any shortfall by obtaining more sleep across the shift cycle, sleeping longer sleep on free days and following morning/evening shifts (Verhaegen *et al.*, 1987; Alward & Monk, 1990; Escribà *et al.*, 1992). While night workers are the most severely impacted in terms of sleep loss, they are not the only shift workers to obtain insufficient sleep. Many studies have found that shift workers commencing early morning day shifts obtain significantly less sleep than shift workers commencing day shifts at 9:00-10:00 h because the circadian system makes it difficult to initiate and maintain sufficiently earlier bedtimes (Ingre *et al.*, 2008; Roach *et al.*, 2012). Aside from shift times, other factors related to shift work schedules may also contribute to sleep disturbances, such as long working hours, reduced rest periods, reduced napping opportunities, backward rotating schedules, and on-call duties, although more field studies are needed to clarify their impacts (Tucker *et al.*, 2000; Akerstedt, 2003; Sallinen & Kecklund, 2010; Ferguson *et al.*, 2016).

In addition to shift characteristics, inter-individual differences may also influence sleep, the response to sleep deprivation and, as a result, the tolerance to shift work schedules (Van Dongen *et al.*, 2004; Van Dongen & Belenky, 2009). The differences in the neurobehavioral response to sleep deprivation may have, at least partially, a genetic origin (Viola *et al.*, 2007; Pellegrino *et al.*, 2014). For example, a polymorphism in the core clock gene *PER3* has been associated with altered sleep homeostasis as well as a greater decline in cognitive performance in response to total sleep loss (Viola *et al.*, 2007). However, the effect of this polymorphism on the decline in cognitive performance could not be replicated in a study that used a chronic partial sleep deprivation paradigm,

which may be due to differences in the effect of total vs partial sleep deprivation and/or other methodological differences (Goel *et al.*, 2009). Furthermore, it remains to be investigated whether inter-individual differences in cognitive performance during sleep deprivation in laboratory settings translate to altered performance in the workplace.

Interestingly, individuals who are resistant to the effects of sleep deprivation, as evidenced by a lower number of attention lapses during psychomotor vigilance tests, also seem to have an altered transcriptomic response during sleep deprivation, with a lower number of rhythmically expressed transcripts, as well as lower amplitudes of rhythmically expressed transcripts (Arnardottir *et al.*, 2014). It has been suggested that this may be an adaptive physiological mechanism that allows the resistant individuals to respond more efficiently to unanticipated sleep-wake states (Warby & Mongrain, 2014). However, the extent to which individuals differ in their metabolic and cardiovascular responses to sleep deprivation, and whether this has a genetic component, requires further exploration.

Despite these individual differences, promoting circadian adaptation to shift schedules is one possible way to mitigate sleep disturbances associated with shift work. For example, in a study from our laboratory, we found that re-establishing a normal phase relationship between the central circadian clock and the shifted sleep period with intermittent bright light exposure on the night shift increased the duration of daytime sleep in nurses (Boivin *et al.*, 2012a).

Metabolic and cardiovascular effects of circadian misalignment and sleep disruption

The circadian system and sleep-wake cycle both contribute to the regulation of metabolism in humans. For example, glucose metabolism (Van Cauter *et al.*, 1991; Shea *et al.*, 2005; Saad *et al.*, 2012; Morris *et al.*, 2015; Poggiogalle *et al.*, 2018), lipid metabolism (Chua *et al.*, 2013; Gooley, 2016), energy expenditure (McHill & Wright, 2017), and substrate utilization (Morris *et al.*, 2015) display endogenous circadian rhythms and are impacted by sleep disturbance, as discussed below. Interestingly, recent evidence indicates that the composition of the human microbiome shows 24-hour variation that is affected by meal timing (Kaczmarek *et al.*, 2017; Collado *et al.*, 2018). The function of the cardiovascular system is also subject to circadian regulation (Martino & Young, 2015; Thosar *et al.*, 2018). Circadian rhythms have been observed in blood pressure, heart rate, as well as in the parasympathetic and sympathetic modulation of the heart (Scheer *et al.*, 2010; Boudreau *et al.*, 2012). In addition, drug-induced changes in cardiac repolarization depend on the time of day (Kervezee *et al.*, 2016). The profound influence of the circadian system on metabolism is supported by metabolomic studies that have shown circadian variation across many classes of metabolites, including amino acids, acylcarnitines, and lipids (Dallmann *et al.*, 2012; Chua *et al.*, 2013; Davies *et al.*, 2014; Giskeodegard *et al.*, 2015; Rhoades *et al.*, 2017). Nevertheless, it should be noted that the relationship between the circadian system and metabolism is bidirectional (Brown, 2016). To ensure optimal synchrony of physiological processes and to match the consistent daily fluctuations in energetic demands posed by the environment, metabolic outputs also feedback onto the clock (Brown, 2016). Circadian misalignment or sleep disturbances can disrupt these intricate relationships and thereby affect metabolic and

cardiovascular health. In the next section, we will review effects of circadian misalignment and sleep disturbances on metabolism and cardiovascular system.

Circadian misalignment

The acute effects of circadian misalignment on metabolism and the cardiovascular system in humans have been studied using various experimental protocols. These studies are typically conducted in healthy, non-shift working participants under controlled laboratory conditions, because circadian misalignment is difficult to quantify in field conditions, as discussed above. Experimental protocols used to study the effects of circadian misalignment include forced desynchrony protocols, in which participants are exposed to non-24-hour sleep-wake and fasting-feeding cycles such that the endogenous circadian timing system becomes desynchronized from the behavioural cycles (Thosar *et al.*, 2018). Circadian misalignment can also be experimentally induced by simulated shift work protocols, in which the sleep period is displaced to the daytime. Under dim light conditions, this leads to circadian misalignment because the endogenous circadian timing system remains aligned to a day-oriented schedule (Boivin & Boudreau, 2014).

Using these types of protocols, the effects of circadian misalignment on metabolic and cardiovascular processes have been characterized. For example, it has consistently been reported that circadian misalignment leads to elevated post-prandial glucose levels and reduced insulin sensitivity (Scheer *et al.*, 2009; Buxton *et al.*, 2012; Gonnissen *et al.*, 2012; Leproult *et al.*, 2014; Eckel *et al.*, 2015; Morris *et al.*, 2015; Bescos *et al.*, 2018). Two studies reported that in a subset of participants, post-prandial glucose levels were elevated to pre-diabetic or diabetic levels during circadian misalignment (Scheer *et al.*, 2009; Buxton *et al.*, 2012). Importantly, reduced insulin sensitivity has not only been

observed in healthy participants, but also in in chronic night shift workers during a laboratory protocol inducing circadian misalignment (Morris *et al.*, 2016b). While the adverse effect of circadian misalignment on post-prandial glucose levels and insulin sensitivity has been consistently observed, the effect on fasting glucose levels is less clear with some studies reporting no effect of circadian misalignment (Scheer *et al.*, 2009; Morris *et al.*, 2015) and others showing increased fasting glucose levels during circadian misalignment (Buxton *et al.*, 2012; Bescos *et al.*, 2018). On a molecular level, it has been found that circadian misalignment protocols affect daily rhythms in genome-wide gene expression levels in blood cells from healthy human subjects, including genes involved in processes such as lipid metabolism (Archer *et al.*, 2014; Kervezee *et al.*, 2018). Archer et al. (2014) reported that the majority of rhythmically expressed genes lose their rhythms during circadian misalignment in a forced desynchrony protocol, whereas we found that the majority of rhythmic genes remain rhythmic but have not adapted to a simulated shift work schedule after four days (Kervezee *et al.*, 2018). This discrepancy is possibly due to the use of different statistical algorithms (Kervezee *et al.*, 2018). However, it is clear from these studies that circadian misalignment induces changes on the transcriptomic level that may affect downstream metabolic processes. In general, it has been proposed that the short-term effects of circadian misalignment on metabolism may contribute to the elevated risk of diabetes and other metabolic problems that has been observed in shift workers (Qian & Scheer, 2016).

Circadian misalignment may also impact energy homeostasis. A simulated night shift work protocol caused a reduction in energy expenditure compared to baseline values (McHill *et al.*, 2014). In line with this, sleep restriction combined with circadian

misalignment was found to reduce resting metabolic rate (Buxton *et al.*, 2012). Several studies have also reported altered substrate utilization during circadian misalignment, including an increase (Gonnissen *et al.*, 2012; Morris *et al.*, 2015) or a decrease (McHill *et al.*, 2014) in carbohydrate oxidation, as well as increased lipid oxidation (McHill *et al.*, 2014; Morris *et al.*, 2015). Furthermore, circadian misalignment reduces 24-hour levels of the appetite-suppressing hormone leptin (Scheer *et al.*, 2009; Buxton *et al.*, 2012), and has recently been shown to significantly increase levels of the appetite-stimulating hormone ghrelin (Qian *et al.*, 2018).

Various studies have found an effect of circadian misalignment on the cardiovascular system, including increased blood pressure (Scheer *et al.*, 2009; Morris *et al.*, 2016a), which seems to be mainly due to increased systolic and diastolic blood pressure during the sleep period (Morris *et al.*, 2016a). Interestingly, also among chronic shift workers, 24-hour systolic and diastolic blood pressure were increased during a laboratory protocol inducing circadian misalignment, with systolic blood pressure being mainly increased during the wake period and diastolic blood pressure being mainly increased during the sleep period (Morris *et al.*, 2017). While one study reported no effect of circadian misalignment on parasympathetic cardiac control (Scheer *et al.*, 2009), a subsequent study by the same group found that parasympathetic cardiac control was decreased during circadian misalignment (Morris *et al.*, 2016a), which could provide a mechanistic explanation for the elevated blood pressure observed during circadian misalignment. Another study reported decreased parasympathetic cardiac modulation across different sleep stages during circadian misalignment combined with sleep restriction, but not during sleep restriction alone (Grimaldi *et al.*, 2016). However, in a study among chronic

shift workers, circadian misalignment did not affect markers of cardiac vagal modulation under controlled laboratory conditions (Morris *et al.*, 2017). In another laboratory study involving rotating shift workers, the sympathovagal balance was found to differ between shift workers whose central circadian clock was not adapted after a week of nights compared to those whose clock was adapted: namely, the sympathetic modulation of the heart was increased relative to the parasympathetic modulation in the non-adapted group compared to the adapted group (Boudreau *et al.*, 2013). These findings may have clinical implications as autonomic imbalance characterized by sympathetic dominance is related to cardiovascular diseases (Thayer *et al.*, 2010). In addition, circadian misalignment affects the levels of inflammatory markers that are risk factors for cardiovascular disease in healthy non-shift working participants (Leproult *et al.*, 2014; Wright *et al.*, 2015; Cuesta *et al.*, 2016; Morris *et al.*, 2016a) as well as in healthy chronic night shift workers (Morris *et al.*, 2017).

Sleep loss and disruption

The consequences of sleep loss on metabolic, endocrine and cardiovascular systems have been widely studied under controlled laboratory conditions as well as in large-scale epidemiological studies (Spiegel *et al.*, 1999; Mullington *et al.*, 2009; Buxton *et al.*, 2010). Cross-sectional and longitudinal epidemiological research has shown an increased risk of type 2 diabetes for individuals obtaining chronically insufficient sleep (Gottlieb *et al.*, 2005; Yaggi *et al.*, 2006; Gangwisch *et al.*, 2007; Beihl *et al.*, 2009; Chaput *et al.*, 2009; Anothaisintawee *et al.*, 2016). Sleep quality is also a risk factor, with studies showing disrupted sleep is associated with an increased risk of diabetes (Meisinger *et al.*, 2005). Attempts to elucidate the mechanisms behind this association using various

protocols of sleep restriction in the laboratory indicate that sleep loss impairs glucose tolerance (Spiegel *et al.*, 1999; Nedeltcheva *et al.*, 2009a; Buxton *et al.*, 2010; van Leeuwen *et al.*, 2010; Reynolds *et al.*, 2012). Indeed, oral and intravenous glucose tolerance tests have revealed significant increases in circulating glucose due to reduced insulin sensitivity or inadequate insulin production after restricting sleep to between 4 and 6 hours per night for as little as a week (Spiegel *et al.*, 1999; Nedeltcheva *et al.*, 2009a; Buxton *et al.*, 2010; van Leeuwen *et al.*, 2010; Reynolds *et al.*, 2012). Recently, it was shown that decreased postprandial insulin sensitivity induced by one night of total sleep deprivation is accompanied by tissue-specific changes in transcriptomic, epigenetic, proteomic, and metabolomic markers that are suggestive of protein breakdown in skeletal muscle and adipogenesis in adipose tissue (Cedernaes *et al.*, 2018), uncovering a potential molecular mechanism that underlies the metabolic changes associated with sleep loss. A cross-sectional field study found that poorer sleep quality was associated with higher insulin and glucose levels, and insulin resistance (Knutson *et al.*, 2006). These findings have been corroborated in the laboratory, with experimentally-induced sleep fragmentation and selective suppression of slow-wave sleep found to cause declines in insulin sensitivity without sufficient compensatory increases in the release of insulin (Tasali *et al.*, 2008; Stamatakis & Punjabi, 2010; Herzog *et al.*, 2013). It was observed that declines in glucose tolerance due to reduced insulin sensitivity were strongly associated with the magnitude of the reduction of slow-wave sleep, indicating an important role of deep sleep in glucose metabolism (Tasali *et al.*, 2008). If allowed to persist, these consequences of sleep loss and sleep disturbance could lead to the

development of a pre-diabetic state and heighten the potential for an eventual diagnosis of diabetes.

Further illustrating the health consequences of sleep loss, chronically sleep-restricted adults are more vulnerable to gaining weight as a consequence of overall increased caloric intake compared to adults who sleep for 7 - 9 hours per night (Nedeltcheva *et al.*, 2009b; Spaeth *et al.*, 2013; Broussard *et al.*, 2016). Markwald et al. (2013) conducted a randomized cross-over study in which participants were scheduled 5-hour or 9-hour of time in bed and permitted unrestricted food access. They found that participants in the sleep restricted group gained more weight than those in the 9-hour condition, despite expending 5% more energy, due to consuming significantly more calories after dinner. The positive calorie balance and weight gain attributed to chronic sleep loss may partly be attributed to changes in the secretion of the appetite-regulating hormones leptin and ghrelin. In several cross-sectional studies, Taheri et al. (2004) and Chaput et al. (2007) observed that short sleep is associated with lower leptin levels and elevated ghrelin levels, with respective decreases and increases of up to 15% in each for habitual sleep durations of 5 hours compared to 8 hours. Though early studies involving total sleep deprivation and chronic sleep restriction in the laboratory appear to corroborate this effect on leptin (Mullington *et al.*, 2003; Spiegel *et al.*, 2004), results from more recent studies are mixed, with sleep loss instead associated with increased leptin levels (Simpson *et al.*, 2010; Reynolds *et al.*, 2012) or no changes (Nedeltcheva *et al.*, 2009b; Broussard *et al.*, 2016). Results about changes in ghrelin levels after sleep loss appear more consistent; indeed, Broussard et al. (2016) found that increased ghrelin concentrations following sleep restriction predicted food intake.

A number of population-based epidemiological studies have reported associations between short sleep and an increased risk of hypertension and cardiovascular (CV) disease in the general population (Ayas *et al.*, 2003; Buxton & Marcelli, 2010; Palagini *et al.*, 2013). Laboratory studies also support a physiological effect of sleep loss on the cardiovascular system; both chronic sleep restriction and acute sleep deprivation have been shown to result in higher blood pressure in normotensive individuals via increases in sympathetic cardiovascular modulation, decreases in parasympathetic cardiovascular modulation, or decreases in the baroreflex – a homeostatic mechanism that helps to maintain blood pressure levels (Zhong *et al.*, 2005; Palagini *et al.*, 2013). Aside from duration, the quality of sleep can also contribute to high blood pressure (Palagini *et al.*, 2013). Numerous population-based studies show that individuals with difficulty initiating sleep, maintaining sleep, or self-reported insomnia combined with short sleep have an increased risk of prevalent and incident hypertension (Palagini *et al.*, 2013). While the precise mechanisms supporting this link between sleep loss and cardiovascular health are not definitive, one pathway is thought to involve the activation of inflammatory processes (Shamsuzzaman *et al.*, 2002). C-reactive protein (CRP) is a stable inflammation marker strongly predictive of cardiovascular disease, and several studies show that both total sleep deprivation and short-term sleep restriction produce pro-inflammatory responses as evidenced by increases in CRP levels (Shamsuzzaman *et al.*, 2002; Meier-Ewert *et al.*, 2004; Van Leeuwen *et al.*, 2009).

Effect of shift work on metabolic and cardiovascular health

Numerous studies have shown that circadian misalignment and sleep restriction independently impact metabolic and cardiovascular processes. Although there are many

additional confounding factors that often arise in shift work, including changes to physical activity and dietary habits (Lowden *et al.*, 2010; Nabe-Nielsen *et al.*, 2011), shift work forms a nexus where circadian misalignment and sleep disturbances consistently occur together. Indeed, the general picture emerging from existing literature is that shift work is associated with adverse cardiovascular and metabolic outcomes (Brum *et al.*, 2015; Kecklund & Axelsson, 2016). In this section, we describe the effect of shift work on metabolic and cardiovascular risk factors and, focusing on recently published meta-analyses and systematic reviews, we review the epidemiological studies that have addressed the association between shift work and metabolic and cardiovascular disease.

Impact of shift work on metabolic and cardiovascular risk factors

Various lines of evidence point towards an adverse effect of shift work on metabolic and cardiovascular risk factors, including elevated glucose, insulin, and triacylglyceride levels, higher counts of white blood cells, as well as increased levels of resistin, a biomarker of atherosclerosis (Sookoian *et al.*, 2007; Burgueno *et al.*, 2010; van Drongelen *et al.*, 2011; Manodpitipong *et al.*, 2017; Wirth *et al.*, 2017). Indeed, a systemic review comprising 22 longitudinal studies on the association between shift work and metabolic risk factors indicated that there is strong evidence for an effect of shift work on impaired glucose tolerance, and the risks of weight gain and being overweight (Proper *et al.*, 2016). Insufficient evidence was available to assess the relationship between shift work and lipid metabolism or blood pressure (Proper *et al.*, 2016). A crude relationship between shift work and body weight change was also reported by van Drongelen et al. in a systematic review involving eight longitudinal studies (van Drongelen *et al.*, 2011). However, only five of the studies considered in this systematic

review adjusted for potentially relevant confounding factors, such as physical activity, gender, age, and/or body weight at baseline, after which the observed effect on body weight change was found to be inconsistent (van Drongelen *et al.*, 2011). These inconsistent results possibly reflect the heterogeneity among the different studies as well as the smaller number of studies that adjusted for confounders. The aforementioned systematic reviews only included longitudinal studies comparing shift workers with non-shift workers regardless of shift type or shift system. Previous studies have shown that specific shift characteristics can affect cardiovascular risk factors. For example, Viitasalo *et al.* (2008) found that changing from a backward-rotating schedule to a forward-rotating shift schedule reduced systolic blood pressure. Interestingly, it was recently reported that night shift work was associated with poorer glycemic control compared to day work or unemployment in diabetic patients, even after controlling for variables such as sleep duration, body mass index, and daily carbohydrate intake (Manodpitipong *et al.*, 2017), supporting an effect of circadian misalignment independent of behavioural changes associated with night shift work in this patient population.

Association between shift work and metabolic and cardiovascular disease

Several recent meta-analyses and systematic reviews have attempted to combine the various epidemiological studies that address the relationship between shift work and metabolic and cardiovascular health, providing evidence for an association between shift work and metabolic syndrome (Wang *et al.*, 2014), diabetes mellitus (Gan *et al.*, 2015), obesity (Sun *et al.*, 2018), hypertension (Manohar *et al.*, 2017), and cardiovascular disease (Torquati *et al.*, 2018). These relationships may be differentially influenced by sex: female shift workers were shown to have a higher risk of developing metabolic

syndrome (Wang *et al.*, 2014), but a lower risk of diabetes mellitus and hypertension compared to male shift workers (Gan *et al.*, 2015; Manohar *et al.*, 2017). In addition, while a rotating shift schedule was associated with an increased risk of diabetes and hypertension compared to other types of shift schedule (including night shifts) (Gan *et al.*, 2015; Manohar *et al.*, 2017), permanent night shift workers showed a higher risk of developing obesity than rotating shift workers (Sun *et al.*, 2018). A recent meta-analysis comprising 21 longitudinal and case-control studies showed that shift work was associated with a heightened risk of cardiovascular disease, specifically coronary heart disease and ischemic heart disease, but not with a risk of other cardiovascular disease morbidity or risk of mortality (Torquati *et al.*, 2018). While some meta-analysis find evidence for a positive dose-response relationship between exposure to shift work and negative health outcomes (Wang *et al.*, 2014; Sun *et al.*, 2018; Torquati *et al.*, 2018), there is a need for high-quality longitudinal studies in order to tease apart the effect of years of exposure, intensity (e.g. number of night shifts per month), and shift schedule on health outcomes (Kecklund & Axelsson, 2016). Improving the understanding of these different aspects of shift work on health outcomes will facilitate the development of strategies that prevent or mitigate the burden of shift work on health and well-being.

Behavioural strategies to minimise the cardiometabolic consequences of circadian disruption and sleep disturbance in shift work

Given that altered rest-activity cycles in shift work mean that some circadian disruption and sleep disturbance is unavoidable, shift workers can proactively implement a variety of lifestyle changes and engage in behaviours that address the metabolic and

cardiovascular risk factors associated with their schedules. This includes engaging in behaviours that attempt to minimize the extent of circadian misalignment and sleep loss directly, as well as behaviours that counteract their ensuing cardiometabolic risks.

Strategic light/dark exposure

One way of minimizing the consequences of circadian misalignment on cardiometabolic health outcomes may be to directly target the misalignment and promote adaptation to night work through strategic light/dark exposure. Light is the strongest signal to the circadian system and can shift the timing of an individual's circadian clock earlier or later, depending on the phase of exposure (Czeisler *et al.*, 1986; Minors *et al.*, 1991); indeed, light prior to the core body temperature minimum delays the clock, while light following the temperature minimum advances the clock. As described earlier, the relative exposure to light before and after this crossing point accounts for about 47% of the variation in phase shifts amongst night workers (Stone *et al.*, 2018). Therefore, knowledge of an individual's circadian clock time relative to the shift schedule and environmental light-dark cycle is critical for optimal implementation of exposure strategies. Nonetheless, a large body of research exists detailing how both bright light and darkness may be used to accelerate the adaptation of the clock to night work (Eastman, 1990; Eastman & Martin, 1999). The overall effectiveness of these timing strategies has been supported in the laboratory (Crowley *et al.*, 2003) and in the field (Boivin *et al.*, 2012b). The spectrum of light exposure, particularly blue light, is also important to consider for the purpose of adaptation because the phase-shifting properties of different wavelengths vary (Wright & Lack, 2001; Wright *et al.*, 2004). It should be noted that depending on the timing and intensity, light exposure can lead to the

suppression of nocturnal melatonin levels. This has a range of metabolic consequences, including but not limited to decreased insulin sensitivity, decreased glucose tolerance, and dyslipidemia (Cipolla-Neto *et al.*, 2014). Therefore, while light may be beneficial in the context of facilitating circadian adaptation to a shift, its use may also have unwanted side-effects on metabolic processes.

Opportunistic napping

Since it can be difficult for shift workers to obtain long consolidated periods of sleep and there is evidence that multiple shorter sleep episodes can be similarly recuperative (Roach *et al.*, 2017), napping may be one way of minimizing overall daily sleep loss and associated cardiovascular and metabolic declines (Akerstedt, 2003; Rotenberg *et al.*, 2016). These naps could be obtained at opportune times during breaks between shifts to supplement main sleep episodes. Alternatively, in industries that allow on-shift napping, these opportunities could be strategically utilised to serve the dual purposes of satiating sleep need and mitigating fatigue (Bonnet, 1991; Rosekind *et al.*, 1995). Recent studies suggest that on-shift napping during the night, if permitted, may protect against hypertension and weight gain by having the added benefit of reducing circadian misalignment (Rotenberg et al., 2016; Silva-Costa et al., 2017).

Physical activity

The benefits of physical activity on health and fitness are well known and there is research to show that exercise also improves sleep duration and sleep quality (Driver & Taylor, 2000; Warburton *et al.*, 2006). As such, increased physical activity is one avenue through which shift workers might forestall and mitigate the cardiometabolic effects of circadian misalignment and sleep loss. To date, researchers have investigated a number of

exercise interventions in the workplace, varying in intensity from extremely vigorous to moderate, of differing effectiveness (Shephard, 1996; Dishman *et al.*, 1998; Kahn *et al.*, 2002; White & Jacques, 2007; Tucker *et al.*, 2016). However, there is very little research on the health outcomes of such interventions for shift workers specifically; where shift workers have been studied, the findings are mixed (Atkinson *et al.*, 2008). In one study, Harma et al. (1988) conducted an exercise intervention for shift working nurses that involved multiple exercise sessions per week over 4 months. They found the exercise group obtained more sleep after evening shifts than the control group; however, they did not observe any differences in body mass or body composition. In a 12-month randomised-controlled interventions study of cleaners, Korshøj *et al.* (2016) found that exercise improved cardiorespiratory fitness, aerobic workload, and resting heart rate. However, there was no discussion about the effectiveness of physical activity by shift type (i.e., morning, afternoon, or evening).

Meal timing and content

Engaging in shift work is often accompanied by changes to eating behaviours (Lowden et al., 2010; Banks et al., 2015). While the preponderance of research indicates that total calorie intake per day does not significantly vary between shift workers and non-shift workers, or between shift types (Reinberg et al., 1979; de Assis et al., 2003; Esquirol et al., 2009; Lowden et al., 2010), shift workers tend to eat larger portions of food with macronutrient contents that are higher in salt, sugar, and fat (de Assis et al., 2003; Esquirol et al., 2009; Heath et al., 2012). Further, snacking behaviour amongst shift workers is more common than amongst non-shift workers, particularly during the night shift (Reinberg et al., 1979; Waterhouse et al., 1997). Although these changes in diet

alone could challenge the effectiveness of individuals' metabolic systems, circadian misalignment exacerbates the risk of health disorders because it disrupts metabolic processes (Al-Naimi et al., 2004; Lowden et al., 2010; Banks et al., 2015). Indeed, consuming food during the night shift is associated with greater body fat (McHill et al., 2017) and can impair postprandial glucose and lipid tolerance (Lund et al., 2001; Al-Naimi et al., 2004; Grant et al., 2017). These findings indicate that another way shift workers could maintain their metabolic and cardiovascular health is to abide by a nutritious diet and avoid consuming food during the night, though this latter suggestion requires further investigation as it may depend on the extent of circadian adaptation to the night shift. To date, research into time-restricted feeding, which refers to the practice of limiting food consumption to a restricted time window (usually less than 12 h) during the day, has been promising for cardiometabolic health outcomes (Longo & Panda, 2016). This type of eating pattern has been reported to have striking health benefits in model organisms as well as in humans, including improved sleep and cardiac function and reduced inflammation and fasting blood glucose levels (Longo & Panda, 2016). For example, reducing the daily food intake duration from more than 14 hours to 10 - 11 hours was effective in reducing body weight in overweight individuals (Gill & Panda, 2015). How this knowledge could be translated to establish beneficial feeding opportunities for shift workers requires further investigation. However, given it may be unreasonable to expect night workers to avoid eating altogether, one approach may be to simply reduce meal sizes. A recent study by Centofanti *et al.* (2018) found that replacing a big snack during the night with a small snack was sufficient to reduce the glucose

response to breakfast, so might be an effective option for minimizing disruption of the metabolic system.

Conclusion and future directions

The cumulative body of research to date clearly illustrates a contribution of shift work to metabolic and cardiovascular health risks. The negative effects of shift work can be, at least partly, attributed to the separate and combined effects of circadian misalignment and sleep loss that often arise, to varying extents, from the altered schedules. The acute physiological effects of circadian misalignment and sleep restriction that have been observed in controlled laboratory studies indeed suggest the involvement of these two factors. Despite this understanding, we are still far from translating this knowledge into practical strategies that may be widely implemented and integrated into the workplace to mitigate the impairment of metabolic and cardiovascular health. High-quality longitudinal studies will allow researchers to address some of the unresolved questions regarding the impact of the duration of exposure to shift work, the intensity of shift work, the type of shift schedule, as well as the effect of age, chronotype, and sex on cardiometabolic health risks. Of particular interest are also the recent advances in chronotherapy, the field of science that aims to optimize drug treatments by taking into account circadian rhythms in physiology. Transcriptomic analysis of human tissues have indicated that the expression of a large proportion of genes encoding drug targets shows diurnal variation (Anafi *et al.*, 2017; Ruben *et al.*, 2018; Ye *et al.*, 2018). An important question in the context of shift workers is to what extent atypical work schedules, and the concomitant circadian misalignment, influence the rhythms in the expression of these

drugs targets and the potential downstream effects on the efficacy of drug treatments. Furthermore, a gap in the current body of research is the lack of understanding regarding the potential mechanisms that link the short-term effects of circadian misalignment and sleep disruption on metabolic and cardiovascular parameters to the health effects that have been observed in shift workers. One candidate mechanism that could provide the missing link is epigenetic changes induced by the altered sleep-wake or feeding behaviour associated with shift work (Aguilar-Arnal & Sassone-Corsi, 2015). Lastly, other avenues for future research include assessments of specific interventions that attempt to minimize circadian misalignment, sleep loss, and their downstream effects on cardiovascular or metabolic processes, such as exercise programs and dietary recommendations. Altogether, these lines of research will contribute to the development of strategies and policies that can be specifically tailored to the workplace and the individual.

Acknowledgments

This work was supported by operating grants from the Canadian Institutes of Health Research (CIHR, MOP-137052) and the Institut de recherche Robert-Sauvé en santé et en sécurité´ du travail (IRSST, operating grant 2013-0046). L.K. received a postdoctoral fellowship from the Fonds de Recherche du Québec–Santé.

Conflict of interest

D.B.B. provides conferences and legal expert advice on various shift work related cases.

The other authors report no conflict of interest.

Abbreviation

SCN - suprachiasmatic nuclei

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Figure

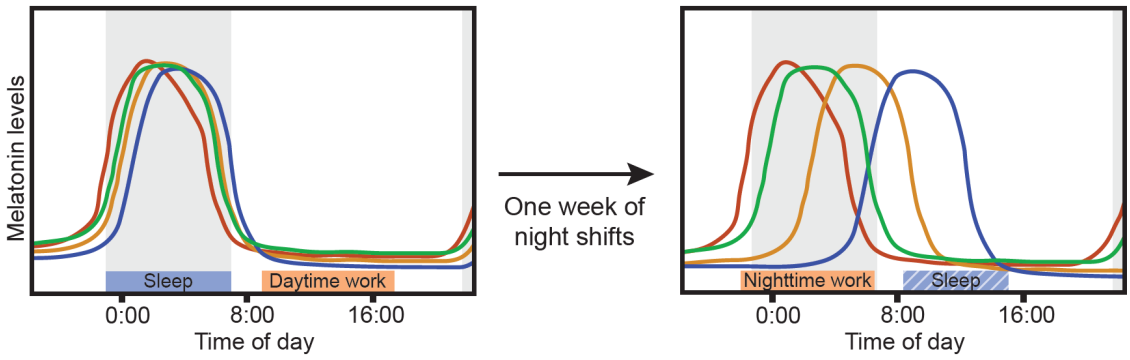

Figure 1. Depiction of theoretical circadian misalignment in night shift workers. Different shaded lines represent melatonin profiles of different hypothetical individuals. Shaded areas represent the habitual sleep period. *Left panel*: during regular daytime work and night-time sleep, the peaks of melatonin profiles occur during the sleep period. *Right panel*: after a period of consecutive night shifts, experimental studies have shown that there is substantial inter-individual variation regarding the melatonin phase, with circadian adaptation occurring in only a small proportion of workers. Due to the shifted work schedule, sleep now occurs outside the biological night, potentially leading to shorter and more fragmented sleep.