Consequences of Circadian Disruption on Cardiometabolic Health

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KEYWORDS

• Circadian rhythms • Diabetes • Cardiovascular disease • Shift work

KEY POINTS

- Circadian disruption can occur when sleep and/or meal timing occurs out of synchrony with the light-dark cycle (environment) or the central circadian clock (endogenous).
- Circadian disruption is associated with increased risk of impaired cardiometabolic function and associated diseases, including obesity, diabetes, and cardiovascular disease.
- Shift work is associated with severe circadian disruption but even milder delays in bedtime or meals are associated with impaired cardiometabolic function.
- Sleep, meal timing, and light at night could link late chronotype and shift work to circadian disruption.

INTRODUCTION

Cardiovascular disease (CVD), diabetes, and obesity affect millions of people worldwide and the rates of these cardiometabolic diseases are on the rise.[1,2] Cardiometabolic diseases are associated with reduced quality of life, lower life expectancy, and increased economic burden on both the individual and on society.[3–6] Therefore, thorough understanding of all the risk factors for these diseases could contribute to improvement in global health. This article discusses a potentially novel risk factor for cardiometabolic disease: circadian disruption.

Circadian disruption occurs when the endogenous circadian (~24-hour) rhythms are not in synchrony with either the environment or each other. This desynchrony can occur when behaviors such as wake, sleep, and meals are not at an appropriate time relative to the timing of the central circadian clock, which is located in the hypothalamus, and/or relative the external environment, particularly the light-dark cycle. This article reviews studies that examined cardiometabolic health of shift work, which typically leads to circadian disruption; studies that experimentally disrupted circadian rhythms to determine the effects on cardiometabolic function; and observational studies that examined sleep timing and behavioral chronotype. A few potential mediators linking the chronotype and shift work to circadian disruption and cardiometabolic health are briefly discussed.

OBSERVATIONAL STUDIES OF SHIFT WORK

Shift work does not have a universal definition but can refer to work shifts that occur always at night (permanent night shift) or rotate between different shifts (day, afternoon, night) across the month. Some studies also include work shifts that are simply outside the standard 9:00 AM to 5:00 PM on

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Monday through Friday. Any work shift that requires an individual to be awake at a time that their central circadian clock associates with sleep has the potential to disrupt that individual's circadian rhythms.

Shift work has been associated with an increased risk of numerous cardiometabolic diseases and their risk factors. Several studies have reported that the risk of developing CVD is higher in shift workers compared with day workers.[7–9] Shift workers also often have higher blood pressure or rates of hypertension than day workers.[10–12] One study found that endothelial function, a marker of CVD risk, was reduced in shift workers.[13] Another study reported abnormalities on the electrocardiogram in the shift workers.[14] Shift workers are also reported to have a higher prevalence or incidence of type 2 diabetes.[15] The longer the history of working as a shift worker resulted in greater the risk of developing diabetes.[16] Another study suggested that the risk of diabetes was mediated by body weight.[17] A meta-analyses of 12 studies with 226,652 total participants, including 14,595 diabetes subjects, found that having ever worked shift work was associated with increased prevalence of diabetes (pooled odds ratio [OR] 1.09, 95% confidence interval [CI] 1.05–1.12).[18] This meta-analyses also found significant sex differences in that the association was stronger in men (OR = 1.37, 95% CI 1.20–1.56) than in women (OR = 1.09, 95% CI 1.04–1.14).

There are several risk factors for CVD, including being overweight or obese, dyslipidemia, insulin resistance, and impaired beta cell function in the pancreas. Individuals performing shift work often have larger body mass indices (BMIs) or waist circumferences than those only working on day shifts.[12,19–24] Several studies have found that shift workers have higher levels of either total cholesterol or triglycerides, or lower levels of high-density lipoprotein (HDL) cholesterol.[12,22,25–29] Other studies have reported alterations in markers of glucose metabolism, including hyperglycemia.[29] One study observed worse estimated beta cell function but no differences in estimated insulin resistance in shift workers compared with day workers.[30] Finally, shift workers are also more likely to have the metabolic syndrome, which is a cluster of metabolic abnormalities that increase the risk of CVD and diabetes, including abdominal obesity, insulin resistance, high blood pressure, and dyslipidemia.[31–33]

It is important to acknowledge that not all studies have reported significant differences between shift workers and day workers on some cardiometabolic measures or all subgroups studied.[14,28,34–37] Differences in results could be due to varying effects of age, sex, definition of shift work, or the duration of shift work.

EXPERIMENTAL CIRCADIAN DISRUPTION

Several studies have experimentally manipulated circadian rhythms in healthy volunteers to determine the effect of circadian disruption on cardiometabolic functions (**Table 1** summarizes these studies). In one study, 10 participants underwent a 10-day forced desynchrony protocol in which they slept and consumed isocaloric meals during a recurring cycle of a 28-hour day.[38] Blood samples were taken hourly to measure levels of leptin, insulin, glucose, and cortisol, and blood pressure was measured 4 times while awake. When participants ate and slept 12 hours off from their habitual times, the maximal circadian misalignment, glucose levels increased by 6%. This was mostly due to postprandial, rather than fasting, levels and the glucose levels were in a prediabetic range in 3 of 8 participants. This increase in glucose occurred despite a 22% increase in insulin levels, suggesting decreased insulin sensitivity with insufficient beta cell compensation. In addition, the circadian rhythm of cortisol was reversed during circadian misalignment with higher levels at the end of a wake episode and at the beginning of a sleep episode, which could also contribute to hyperglycemia. Circadian misalignment was also associated with a 3% increase in mean arterial pressure during wakefulness. Finally, leptin is a satiety signal involved in appetite regulation and the levels of leptin decreased by 17% after circadian disruption. This study demonstrated numerous changes in markers of cardiometabolic function and could explain some of the observed differences between shift workers and day workers.

A second experimental study of circadian disruption also used the 28-hour day forced desynchrony protocol but with concurrent sleep restriction (5.6 hours/24 hours) for 3 weeks to explore the combined effects of sleep restriction and circadian disruption as commonly experienced by shift workers, followed by 9-day recovery period.[39] They enrolled 21 participants; 11 were younger (mean age 23) and 10 were older (mean age 60). Circadian disruption combined with sleep restriction was associated with an 8% increase in fasting glucose levels and a 14% increase in postprandial glucose levels in response to a standardized breakfast. There was an inadequate pancreatic beta cell response because fasting and postprandial peak insulin levels were significantly reduced (by 12% and 27%,