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%,

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respectively). Circadian disruption combined with sleep restriction also decreased the resting metabolic rate by 8%. The 24-hour levels of leptin were slightly lower after circadian disruption combined with sleep restriction, and ghrelin, which is an orexigenic hormone involved in appetite regulation, were slightly higher. These metabolic changes did not differ significantly between the older and younger participants. These results suggest additional details on potential underlying mechanisms of increased diabetes and obesity risk in shift workers.

A third experimental study was designed to determine whether circadian disruption impairs cardiometabolic function independently from the effects of sleep loss using a parallel group design.[40] One group was allowed 5 hours in bed for 8 days with bedtimes always centered at 03:00 hour (circadian aligned) and the second group had 5 hours in bed but on 4 days the bedtimes were delayed by 8.5 hours (circadian misaligned). Both the circadian aligned and misaligned groups had significantly reduced insulin sensitivity without compensatory insulin response. Furthermore, in the men, the decrease in insulin sensitivity was twice as large when circadian misaligned compared with the circadian-aligned group (there were too few women to examine separately). High-sensitivity C-reactive protein (hs-CRP), which is a marker of inflammation, increased in both groups but increased substantially more in the circadian misaligned group (+146 $\pm$ 103% vs +64 $\pm$ 63%, $P = .049$). The results of this experimental study support an independent effect of circadian disruption on glucose metabolism and cardiometabolic risk.

Eating at a circadian-inappropriate time (ie, at night) in humans is commonly seen in shift workers and may play a role in the obesity risk. One study simulated shift work to examine the effects on energy metabolism using a whole-room calorimeter.[41] This 6-day inpatient study simulated shift work in 14 adults by having 2 daytime shifts with 8-hour nocturnal sleep opportunity followed by the first night shift, which only allowed a brief 2-hour sleep opportunity, and then 2 additional night shifts with 8-hour sleep opportunities during the day. Compared with baseline, total daily energy expenditure was 4% higher on the first night shift but 3% lower on the 2 subsequent nightshifts. The thermic effect of feeding (ie, energy expenditure after food intake) was lower in response to late dinner on the first night shift. Subjective appetite decreased during nightshifts despite a decrease in levels of leptin and peptide-YY, another anorexigenic hormone. The combination of decreased energy expenditure and lower thermal effect of feeding after late meals could explain increased obesity in shift workers who often eat at night.

A final experimental study was designed to distinguish the effects of the behavioral cycles (sleep-wake, fasting-feeding, and activity), the endogenous circadian system, and circadian disruption on glucose metabolism.[42] The protocol involved 2 8-day crossover studies when the behavioral cycles were aligned or misaligned (12-hour shift) with their endogenous circadian system. Glucose tolerance was assessed at 8 AM and 8 PM in response to an identical mixed meal along with a measurement of lipids. Postprandial glucose levels were 17% higher in the biological evening than morning and the early phase postprandial insulin response was 27% lower in the evening, indicative of insufficient beta cell response. This endogenous circadian effect was much larger than that of the behavioral cycle effect (8% higher postprandial glucose and 14% lower insulin responses at dinner time compared with breakfast time). In addition, circadian misalignment (12-hour behavioral cycle inversion) increased postprandial glucose levels by 6% despite a 14% higher late-phase postprandial insulin response, suggesting reduced insulin sensitivity during misalignment. This study demonstrates the relative importance of the endogenous circadian system, the behavioral cycle, and circadian misalignment on glucose metabolism.

In summary, these experimental studies have demonstrated the importance of the circadian system and the timing of behaviors such as eating in controlling metabolism, and have provided insights into the mechanisms linking circadian disruption to increased cardiometabolic disease risk.

Circadian disruption contributes to increased cardiometabolic risks. Circadian misalignment results in

1. Impaired glucose tolerance as a result of decreased insulin sensitivity and inadequate beta cell response
2. Elevated inflammatory markers
3. Elevated mean arterial pressure
4. Decreased energy expenditure

OBSERVATIONAL STUDIES OF MILDER CIRCADIAN DISRUPTION

Shift work can be an extreme form of circadian disruption but circadian disruption in milder forms

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Table 1
Circadian disruption experiments in healthy volunteers with evaluation of cardiometabolic changes

Study	Number of Subjects	Protocol	Assessments[a]	Results
Scheer et al,[38] 2009	10	10-d forced desynchrony protocol of 28-h day, consisted of 2 baseline days (8-h habitual sleep) followed by 7 recurring 28-h sleep-wake cycles under dim light conditions, with 4 isocaloric meals during each cycle Ratio of scheduled sleep to wake was maintained at 1:2	• Hourly sample of plasma leptin, insulin, glucose, cortisol • Blood pressure	During circadian misalignment (subjects ate and slept 12 h from their habitual time): • Leptin decreased by 17% • Glucose increased by 6% (from postprandial rather than fasting levels) and insulin increased by 22%, suggesting decreased insulin sensitivity and insufficient pancreatic beta cell response • Mean arterial pressure increased by 3 mm Hg during wakefulness • Reversal of daily cortisol rhythm
Buxton et al,[39] 2012	21 (11 mean age 23 y, 10 mean age 60 y)	3 wk of forced desynchrony (28-h day) with 5.6-h/24 h sleep restriction, followed by 9 recovery days (24-h) with 10-h sleep opportunity/d	• Glucose and insulin response to standardized breakfast • RMR • 24-h profile of leptin and free ghrelin	At the end of concurrent sleep restriction and circadian disruption: • Glucose levels increased, both fasting (by 8%) and postprandial (by 14%); these returned to baseline after 9-d recovery period • Decreased fasting and postprandial peak insulin levels, reflecting inadequate pancreatic beta cell function • RMR decreased by 8% • Leptin profiled slightly decreased and free ghrelin profile slightly increased; these also occurred during recovery compared with baseline • Overall, no significant differences in these metabolic changes between younger and older participants
Leproult et al,[40] 2014	26 (19 male)	A parallel design comparing 8-d of sleep restriction (5 h) and sleep restriction combined with circadian misalignment (5-h bedtime with 8.5 sleep onset delayed for 4 of 8 d)	• Intravenous glucose tolerance test at baseline and the end of the experiment • Inflammatory marker hs-CRP measurement	At the end of the experiment: • Insulin sensitivity decreased from baseline in both circadian aligned and misaligned groups; this was not compensated by increased beta cell response • Men in the misaligned group had twice as large reduction in insulin sensitivity compared with the aligned group; differences in women were not apparent possibly due to small number of participants • hs-CRP increased significantly in misaligned group; in men, the misaligned group had levels more than doubled those of aligned group

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McHill et al,[41] 2014	14	6-d inpatient simulated nightshift protocol (3-d daytime schedule followed by 3-d nightshift schedule), conducted in a whole-room calorimeter	• EE • Energy expenditure after meal (TEF) • Macronutrient use • Appetite rating, leptin, peptide-YY and ghrelin	During nightshifts: • EE decreased by 3% • TEF decreased in response to late dinner on first nightshift • Total fat use increased, and carbohydrate and protein use decreased • Appetite rating was lower despite lower levels of leptin and peptide-YY; ghrelin was unchanged
Morris et al,[42] 2015	14	Two 8 d of circadian aligned and circadian misaligned to evaluate the relative effects of behavioral cycle, endogenous circadian system and circadian misalignment on glucose and lipids metabolism	• Glucose, insulin and FFA responses to standard mixed meal test at 8 AM and 8 PM	• Postprandial glucose was 17% higher in the biological evening than morning, with 27% reduction in early phase postprandial insulin response, indicative of insufficient beta cell response • These changes were larger than the effects of the behavioral cycle • Circadian misalignment resulted in reduced glucose tolerance with increased later-phase insulin secretion, suggesting increased insulin resistance • FFA higher before dinner than breakfast time, and higher during circadian misalignment

Abbreviations: EE, total daily expenditure; FFA, free fatty acid; hs-CRP, high-sensitivity C-reactive protein; RMR, resting metabolic rate; TEF, thermal effect of feeding.

[a] Some studies had additional assessments. Please refer to references listed.

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can also be detrimental. For example, going to bed at a different time on work or school days than on free days or weekends can lead to social jet lag, which may also be associated with cardiometabolic function. Also, the clock time that someone goes to bed, which can be a measure of chronotype, may be associated with cardiometabolic function. Finally, the time of day someone prefers to sleep versus be active, often called circadian preference, may be another characteristic of chronotype associated with cardiometabolic health. In this section, the association between cardiometabolic function and social jet lag and chronotype is discussed.

Many individuals in modern society experience social jet lag because of obligations such as work or school that require a specific wake time, and this obligation is lifted on free days.[43] In a large epidemiologic survey of more than 65,000 participants, greater social jet lag was associated with being overweight (BMI $\geq$25 kg/m^2).[44] In addition, among overweight participants, there was a positive correlation between social jet lag and BMI; those who slept at a later clock time had a higher BMI. Subsequent studies have demonstrated an association between social jet lag and adverse cardiometabolic profiles. In a study of 145 healthy participants, those with a social jet lag greater than or equal to 2 hours had significantly higher fasting morning cortisol and higher area-under-the-curve of cortisol levels collected over 5 hours starting in the morning.[45] Those with a social jet lag greater than or equal to 2 hours also had higher resting heart rate, shorter average sleep duration, and less physical activity. In a larger study of 815 non–shift workers, participants with greater social jet lag were more likely to be obese (OR 1.2, 95% CI 1.0–1.5) and to have the metabolic syndrome (OR 1.3, 95% CI 1.0–1.6).[46] Furthermore, among those who were obese and had the metabolic syndrome, greater social jet lag was also associated with an increased odds of having elevated glycated hemoglobin ($\geq$5.7%) and elevated inflammation (hs-CRP levels>3 mg/L).[46]

Individuals with a later chronotype, that is, those who sleep at a later clock time, often have a greater degree of circadian misalignment between behavioral rhythms and the endogenous central circadian clock, and they also often have greater social jet lag.[43] A later (evening) circadian preference and later chronotype have been associated with several cardiometabolic disorders and unhealthy behaviors (**Table 2**). In adolescents, large population studies have shown that those with evening circadian preference or later bed and wake times had a higher BMI z score, increased risk of being obese (OR 2.16), and less time spent in moderate-to-vigorous physical activity.[47,48] An unhealthy diet may partly play a role in this association because those with evening preference were reported to have worse dietary habits, including frequent snacking, less fruits and vegetables consumption, increased caloric intake from fat, and meal skipping.[48–51] In an 8-week prospective study of 159 college freshmen, students who were evening types gained more weight than those who were morning types.[52]

In addition to obesity, having a later chronotype is also associated with increased cardiovascular risk. For example, obese short sleepers with an evening chronotype had higher stress hormone levels (24-hour urinary epinephrine and plasma corticotropin levels) and higher resting heart rates.[51] Two large population-based studies of more than 6000 participants revealed that evening chronotype was associated with increased odds of having type 2 diabetes (OR 1.73[53] and 2.5 in men and women combined[54]). Evening chronotype was also associated with increased odds of having arterial hypertension (OR 1.3).[54] In addition, in a clinic-based study of 194 subjects with type 2 diabetes, later chronotype based on bedtimes was associated with poorer glycemic control independently of sleep duration.[55] Subsequent studies in type 2 diabetes subjects (total 826 participants) have confirmed the association between evening chronotype and poorer glycemic control.[56,57] Evening chronotype in type 2 diabetes subjects was also associated with higher triglycerides and lower HDL levels.[57]

These studies suggest that milder forms of circadian disruption, not just the more extreme circadian disruption observed in shift workers, are associated with adverse cardiometabolic function. Future research should explore whether interventions to reduce circadian disruption and/or advancing bedtimes can improve cardiometabolic health.

POTENTIAL MEDIATORS LINKING EVENING CHRONOTYPE OR SHIFT WORK AND CARDIOMETABOLIC DISEASE

There are a few potential mediators linking evening chronotype and shift work to circadian disruption and ultimately to cardiometabolic disease (**Fig. 1**). These include reduced sleep duration or quality, inappropriate timing of meals, and light at night. These potential mediators and their associations with cardiometabolic disease are briefly reviewed.

Sleep

Chronotype and shift work is often associated with reduced sleep duration and quality.[16,45] Previous research has demonstrated that inadequate sleep durations, including short sleep, as well as poorer

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sleep quality are associated with cardiometabolic disease. Several meta-analyses of existing studies found that short sleep is associated with increased odds of prevalent obesity,[58] prevalent metabolic syndrome,[59] prevalent hypertension,[60] incident type 2 diabetes,[61] incident hypertension in those less than 65 years old,[60] and increased risk of developing or dying of coronary heart disease (CHD).[62] Furthermore, poor sleep quality has also been associated with increased risk of incident type 2 diabetes.[61] The association between sleep and cardiometabolic disease has been reviewed extensively.[63,64] Thus, impairments in sleep could partially mediate the association between shift work or chronotype and cardiometabolic disease.

Meal Timing

The timing of meals can affect internal circadian alignment because food metabolites serve as synchronizing signals for the clocks in many peripheral tissues and organs.[65] Exposure to food at an inappropriate time of day could lead to misalignment between central and peripheral clocks, which could impair metabolism and lead to weight gain.[66] Indeed, in an experimental model, mice fed at the wrong time of day gained more weight than mice with access to food at the appropriate circadian time despite similar food intake and physical activity.[67]

Studies in humans have also observed a relationship between meal timing and altered metabolism. A randomized crossover study in 32 women compared the effects of eating an early lunch (13:00) to a late lunch (16:30). Compared with the early lunch, the late lunch was associated with decreased pre-meal resting-energy expenditure, decreased pre-meal carbohydrate oxidation, decreased thermal effect of food, as well as decreased glucose tolerance to meal.[68] Decreased energy expenditure and decreased glucose tolerance are risk factors for weight gain and diabetes and, therefore, these results provide evidence for a link between eating at a later clock time and metabolic disease. Another study found that more calories consumed after 20:00 was associated with higher BMI, even after controlling for sleep timing and duration.[69] Studies of weight loss interventions have also demonstrated the importance of timing of food intake. In a 20-week weight loss study of 420 participants, those who consumed their main meal (lunch in this Mediterranean population) before 15:00 lost 2.2 kg more on average than those who ate after 15:00, despite consuming similar amount of calories.[70] In a second weight loss study, women were randomized to either a large proportion of calories earlier in the day (70% for breakfast, morning snack, and lunch and 30% for afternoon snack and dinner) or a more even distribution (55% for breakfast through lunch and 45% for afternoon snack and dinner) for 3 months.[71] Those who eat more food earlier in the day lost significantly more weight (-8.2 vs -6.5 kg, $P = .028$), reduced waist circumference by more (-7 vs -5 cm, $P = .033$), lost more fat mass (-6.8 vs -4.5 kg, $P = .031$), and improved their insulin sensitivity more. A qualitative study found that a strategy used by individuals who maintained 10% weight loss for at least 1 year was eating a small dinner, a strategy not used by individuals who regained weight after an initial loss.[72] Finally, because glucose tolerance is known to be worse in the evening,[73] late eating may also affect glycemic control in patients with diabetes. In fact, a study of patients with type 2 diabetes demonstrated that a greater amount of daily calories consumed at dinner was associated with poorer glycemic control, independently of chronotype.[55] Interestingly, a recent randomized crossover study in type 2 diabetes patients compared a hypoenergetic diet of 2 larger meals (breakfast and lunch) to 6 smaller meals in 54 patients for 12 weeks. Two larger meals resulted in a significantly greater reduction in body weight, liver fat content, fasting plasma glucose, C-peptide, and glucagon, and higher insulin sensitivity, than the same caloric restriction split into 6 meals,[74] indicating the timing of food intake has an important effect on metabolism.

Another potentially important meal pattern is breakfast skipping. There is overwhelming evidence that breakfast skipping is detrimental to health, including higher risks of overweight and obesity, increased visceral adiposity, insulin resistance, type 2 diabetes, and dyslipidemia. For example, a longitudinal study of 2184 participants over 20 years found that those who skipped breakfast in both childhood and adulthood had significantly greater waist circumference and higher fasting insulin, total cholesterol, and low-density lipoprotein cholesterol than those who consumed breakfast at both time points.[75] A study of 3598 participants from the community-based Coronary Artery Risk Development in Young Adults (CARDIA) study found that, relative to those with infrequent breakfast consumption (0–3 days/week), participants who reported eating breakfast daily gained 1.9 kg less weight over 18 years ($P = .001$), along with significant reduction in the incidence of obesity, metabolic syndrome, and hypertension.[76] Moreover, in a cohort of 26,902 American men, those who skipped breakfast had a 27% higher risk of CHD compared with men who did not.[77] In addition

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Table 2
Studies of the associations between chronotype and metabolic outcomes

Study	Population	Number of Subjects	Chronotype Assessments	Metabolic Outcomes
Arora & Taheri,[48] 2015	Young adolescents (aged 11–13 y)	511	Morningness-eveningness questionnaire	• Evening chronotype was associated with higher BMI z score than morning chronotype • Later chronotype was associated with unhealthy diet (snacks, night-time caffeine, and inadequate fruits and vegetables consumption)
Olds et al,[47] 2011	Adolescent (aged 9–16 y)	2200	Bedtime and wake time Participants categorized into: Early-bed, early-rise Early-bed, late-rise Late-bed, early-rise Late-bed, late-rise	• Late-bed, late-rise participants had more screen time by 48 min/d and 27 min less moderate-to-vigorous physical activity than early-bed, early-rise, despite similar sleep duration • Late-bed, late-rise participants had higher BMI z score and were 2.16 times more likely to be obese compared with early-bed, early-rise
Sato-Mito et al,[49] 2011	Young adults (aged 18–20 y)	3304	Midpoint of sleep	• Late midpoint of sleep negatively correlated with unhealthy dietary habits, including increased caloric intake from alcohol and fat with decreased protein and vitamins and minerals consumption • Late midpoint of sleep was associated with meal skipping and watching TV at mealtime
Culnan et al,[52] 2013	College freshmen (mean age 18 y)	159	Morningness-eveningness questionnaire	• Evening types had significantly more BMI gain at 8 wk follow-up compared with morning type
Lucassen et al,[51] 2013	Obese adults with <6.5 h of sleep	119	Morningness-eveningness questionnaire	• Eveningness was associated with fewer and larger meals, lower HDL cholesterol, more sleep apnea and higher stress hormones (24-h urinary epinephrine and morning plasma corticotropin), and higher morning resting heart rate

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Nakanishi-Minami et al,[94] 2012	Adults	32 healthy, and 74 T2DM	Bedtime and wake time	• T2DM patients had significantly later bedtime on weekdays and weekends (by 49 and 68 min, respectively) than those without diabetes • T2DM patients woke up significantly later than those without diabetes, by 31 min on weekdays and 34 min on weekends
Merikanto et al,[54] 2013	Adults, aged 25–74 y	4589	Modified Morningness-eveningness questionnaire	• Evening types had increased risk of having T2DM (2.5-fold) and arterial hypertension (1.3-fold)
Yu et al,[53] 2015	Adults, aged 47–59 y	1620	Morningness-eveningness questionnaire	• Men with evening types had increased risk of having diabetes (OR 2.98) • Women with evening types had increased risk of having metabolic syndrome (OR 1.74)
Reutrakul et al,[55] 2013	Adults with T2DM	194	Mid sleep time on free day corrected for sleep debt	• Later chronotype was independently associated with poorer glycemic control; the association was partially mediated by greater percentage of total daily calories consumed at dinner
Iwasaki et al,[56] 2013	Adults with T2DM	101	Morningness-eveningness questionnaire	• More evening preference was associated with poorer glycemic control (hemoglobin A1c levels) and poorer sleep quality
Osonoi et al,[57] 2014	Adults with T2DM	725	Morningness-eveningness questionnaire	• Eveningness was associated with poorer glycemic control, higher triglycerides, and lower HDL cholesterol levels

Abbreviation: T2DM, type 2 diabetes.

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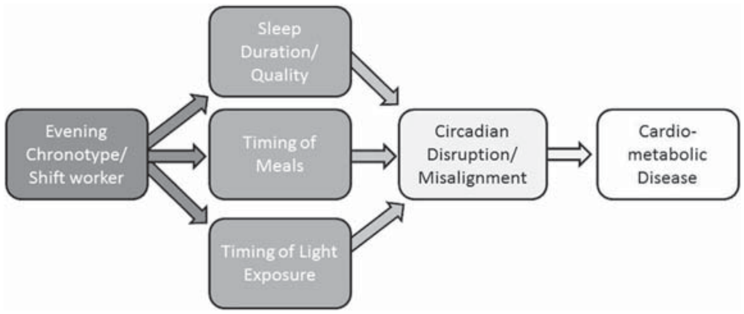

Fig. 1. Potential pathways leading from later chronotype or shift work to circadian disruption and cardiometabolic disease.

men who ate after going to bed had a 55% higher CHD risk than men who did not. However, once adjusting for health factors, such as BMI, hypertension, hypercholesterolemia, and diabetes status, the associations were no longer significant. Another longitudinal study of 29,206 men reported that breakfast skipping was associated with a 21% increase in risk of developing type 2 diabetes, even after adjustment for BMI[78] and the Nurses' Health Study of women also observed a significant association between breakfast skipping and incident diabetes.[79] A recent meta-analysis of 106,935 participants found that breakfast skipping was associated with type 2 diabetes.[34,80] In addition, in patients with type 2 diabetes, breakfast skipping was found to be associated with poorer glycemic control.[50,81,82] A recent study in Japan examined the combination of breakfast skipping and late-night eating and found that a combination of breakfast skipping and late-night eating (consumed dinner within 2 hours of bedtime $\geq$3 times/week) was associated with the presence of the metabolic syndrome (OR 1.17), whereas breakfast skipping or late-night eating alone was not.[83] Finally, a weight-loss intervention study found that eating breakfast was associated with greater weight loss despite similar caloric restriction[84] but a second intervention study found no effect of breakfast eating recommendations.[85]

Overall, the evidence suggests a relationship between meal timing or daily food distribution and cardiometabolic risk. Although breakfast skipping and eating at night are associated with adverse cardiometabolic profiles, more interventional studies are needed to demonstrate whether manipulating meal timing will result in improved metabolism.

Light at Night

Another potential mediator between late chronotype or shift work and cardiometabolic disease is exposure to artificial light at night. Light is the primary synchronizer of the central circadian clock and, therefore, exposure to light during the biological night could lead to circadian disruption. There is some evidence from animal studies that exposure to light at night can impair metabolism. In these studies, male mice that were exposed to a high fat diet and dim light at night had increased weight gain, reduced glucose tolerance, and altered insulin secretion compared with mice that were not exposed to light at night, despite equivalent caloric intake.[86] Furthermore, the timing of the food intake was shifted when exposed to light,[87] indicating that animals exposed to light at night may also be eating more food at an inappropriate circadian time.

Another mechanism through which light at night could impair cardiometabolic function is through melatonin. Melatonin is a hormone primarily secreted by the pineal gland and its release is suppressed by light. Melatonin plays an important role in circadian physiology[88] and also plays a role in sleep promotion.[89] More recently, melatonin has been recognized as playing an important role in metabolism.[90,91] Lower melatonin levels were associated with increased risk of incident diabetes in a large cohort study.[92] Thus, individuals who stay up later will be exposed to more artificial light, which will suppress melatonin and potentially reduce the total amount of melatonin secreted, putting them at risk of diabetes.

The role artificial light may play in health was recently recognized by the American Medical Association (AMA). In June, 2012, the AMA House of Delegates adopted a policy statement on nighttime lighting. The Executive Summary states, "Other diseases that may be exacerbated by circadian disruption include obesity, diabetes…"[93] Thus, there is recognition that electric light could lead to circadian disruption, which, in turn, could impair human health.

SUMMARY

Circadian disruption is associated with impairments in cardiometabolic function and increased

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risk of obesity, diabetes, and CVD. This association is not only among the most severe forms of circadian disruption (ie, shift work), but is also observed with milder delays in the timing of sleep and meals. Future research should determine whether manipulating the timing of sleep, meals, or light exposure can help to improve cardiometabolic health.

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