

## AHA SCIENTIFIC STATEMENT

# Role of Circadian Health in Cardiometabolic Health and Disease Risk: A Scientific Statement From the American Heart Association

Kristen L. Knutson, PhD, FAHA, Chair; Debra D. Dixon, MD, MS; Michael A. Grandner, PhD, MTR, FAHA; Chandra L. Jackson, PhD, MS; Christopher E. Kline, PhD, FAHA; Lisa Maher, DNP; Nour Makarem, PhD, FAHA; Tami A. Martino, PhD; Marie-Pierre St-Onge, PhD, FAHA; Dayna A. Johnson, PhD, MPH, FAHA, Vice Chair; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifelong Congenital Heart Disease and Heart Health in the Young

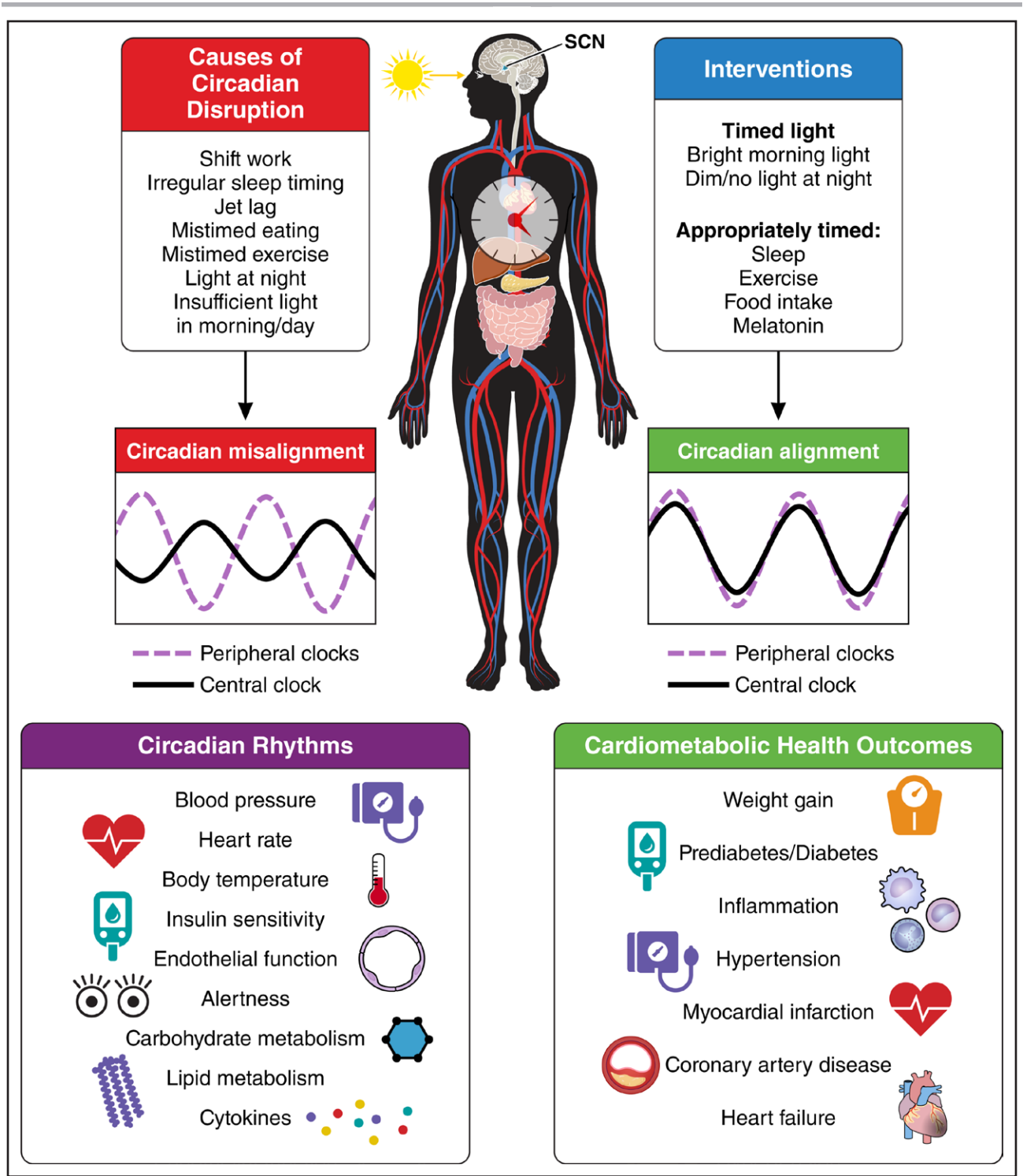
**ABSTRACT:** Cardiovascular and metabolic health are influenced by the circadian system, which regulates 24-hour rhythms across numerous physiologic processes. Disruptions to circadian rhythmicity can adversely affect cardiometabolic function and health. Given the importance of circadian health to overall human health, this scientific statement provides an overview of the circadian system and key behavioral factors that can synchronize or desynchronize these rhythms, including light exposure, food intake, physical exercise, and sleep timing. We also summarize the literature on associations between circadian health and cardiometabolic health indicators, such as excessive weight, type 2 diabetes (T2D), hypertension, and cardiovascular disease. We discuss strategies to improve circadian health and reduce circadian disruptions, focusing on interventions that target the key synchronizers of circadian rhythms and involve appropriate timing of exposure to these synchronizers. These include morning bright light exposure and avoidance of light at night, as well as appropriately timed sleep, meals, and exercise. Clinicians, researchers, policymakers, and the public should recognize the role of circadian rhythms in maintaining and promoting cardiometabolic health and focus on identifying modifiable behaviors that can improve them.

**Key Words:** AHA Scientific Statements ■ cardiovascular diseases ■ circadian rhythm ■ diabetes mellitus, type 2 ■ exercise ■ hypertension

**H**uman physiology is partially regulated by the circadian system, which produces ≈24-hour rhythms adapted for daytime activity and nighttime rest. These rhythms influence cardiometabolic health by regulating metabolism, vascular function, and cardiac performance, among other processes. For example, heart rate, blood pressure (BP), cholesterol synthesis, inflammatory cytokine expression, and autonomic output all exhibit 24-hour patterns,<sup>1,2</sup> as do adverse cardiovascular events, such as myocardial infarction and arrhythmias (see the Figure for additional examples).<sup>3</sup> However, unlike rhythms that are diurnal, or driven by external cues such as light or behavior, circadian rhythms are endogenous and persist even in the absence of such cues (see Table 1 for a glossary of key terms related to the circadian system). Whereas diurnal rhythms reflect the environment we live in and are highly relevant for the practice of medicine,

distinguishing them from circadian rhythms is important for understanding underlying physiology. Disruptions to the circadian system can contribute to cardiometabolic dysfunction and disease progression and circadian health promotion may support cardiometabolic health. Circadian health refers to the optimal function, rhythmicity, and alignment of the circadian system to the light–dark cycle for maintaining physiologic and behavioral homeostasis.

The circadian system includes a central clock in the hypothalamic suprachiasmatic nucleus and peripheral clocks found throughout the body, including cardiovascular and metabolic systems<sup>4,5</sup> (Table 1). Several genes and their proteins constitute the molecular cellular clocks (see Costello and Gumz<sup>6</sup> for more details). The primary synchronizer (termed “zeitgeber” [German for “time giver”]) for the suprachiasmatic nucleus is light



**Figure. Circadian disruption, interventions, and cardiometabolic health outcomes.** The circadian system is synchronized to the external light–dark cycle primarily through light detected by the retina. This light signal is transmitted to the suprachiasmatic nucleus (SCN) in the hypothalamus, which is considered the central circadian clock. Circadian disruption can result from various factors that cause misalignment of circadian rhythms, including those regulating processes necessary for cardiometabolic health. Interventions aimed at improving circadian alignment use signals that can resynchronize both central and peripheral clocks, thereby promoting circadian alignment and supporting cardiometabolic health.

through the retina, which aligns internal rhythms with the external day–night cycle.<sup>4</sup> In turn, the suprachiasmatic nucleus synchronizes peripheral clocks through neural and hormonal signals, such as autonomic nervous system activity and glucocorticoid rhythms.<sup>4</sup> Outputs from the peripheral clocks can also provide feedback to the

Table 1. Key Terms Related to the Circadian System

| Term                     | Description relative to circadian biology   |
|--------------------------|---|
| Acrophase                | Characteristic of a rhythm: the peak of a rhythm or the time when it occurs   |
| Amplitude                | Characteristic of a rhythm: the difference in the level between peak and mean level (or peak and trough)  |
| Autonomic nervous system | Regulator of involuntary functions (eg, heart rate, blood pressure) contributing to circadian control of cardiovascular and metabolic processes   |
| Cardiometabolic health   | Overall health of the cardiovascular and metabolic systems, including heart function, energy regulation, and vascular dynamics  |
| Central circadian clock  | Located in the suprachiasmatic nucleus of the hypothalamus; regulates circadian rhythms and synchronizes peripheral clocks in tissues and organs, including the cardiovascular system   |
| Chrononutrition          | Field that addresses the complex relationship among timing of nutrient intake, circadian rhythms, and health  |
| Chronotherapy            | Therapy focusing on the optimal timing of therapy (eg, timing of medication administration)   |
| Chronotype               | An individual's natural preference for activity and sleep timing, influenced by their internal circadian clocks; often categorized as morning, intermediate, or evening types   |
| Circadian clocks         | Molecular circadian clocks found in the suprachiasmatic nucleus of the hypothalamus (the central clock) as well as in tissue and cells throughout the body (peripheral clocks)  |
| Circadian disruption     | Misalignment of internal clocks (eg, central, peripheral), or between internal rhythms and the external environment (eg, jet lag, rotating shift work); also called desynchrony or circadian misalignment   |
| Circadian health         | Optimal function, rhythmicity (including amplitude), and alignment of the circadian system to the light–dark cycle for maintaining physiologic and behavioral homeostasis   |
| Circadian mechanism      | Genes and proteins (eg, CLOCK [circadian locomotor output cycles kaput], BMAL1 [brain and muscle ARNT-like 1], PER [period], CRY [cryptochrome], REV-ERB [nuclear receptor subfamily 1, group D, member 1; nuclear receptor subfamily 1, group D, member 2]) that drive the circadian feedback loop, regulating ≈24-h rhythms in virtually all cells, including cardiometabolic tissues |
| Circadian medicine       | A rapidly advancing field of medicine focused on applying insights from circadian biology to the prevention, diagnosis, and treatment of diseases, with particular relevance to cardiometabolic disorders (eg, hypertension, diabetes, cardiovascular disease), offering the potential to greatly improve patient outcomes and longevity  |
| Circadian misalignment   | See Circadian disruption  |
| Circadian phase          | A specific point on a rhythm that can be used to determine endogenous circadian timing (eg, temperature nadir, DLMO [see melatonin])  |
| Circadian phase advance  | When the timing of a rhythm becomes earlier (eg, DLMO moving from 9:00 PM to 8:00 PM)   |
| Circadian phase delay    | When the timing of a rhythm becomes later (eg, DLMO moving from 9:00 PM to 10:00 PM)  |
| Circadian rhythm         | Internal ≈24-h cycles regulating physiologic and behavioral processes, synchronized to environmental cues such as light and nutrient intake, characterized by amplitude, phase, and nadir; endogenously driven and controlled by the circadian clock  |

(Continued)

Table 1. Continued

| Term                                  | Description relative to circadian biology  |
|---------------------------------------|--|
| Circadian rhythm sleep–wake disorders | Disorders characterized by either misalignment between sleep–wake patterns and the external light–dark period or disruption of internal circadian clocks (eg, delayed sleep–wake phase disorder, advanced sleep–wake phase disorder, non–24-h sleep–wake rhythm disorder)  |
| Cortisol                              | Hormone with strong circadian rhythm, peaking in the morning, reflecting circadian and stress rhythms  |
| Diurnal rhythms                       | Rhythms aligned with the 24-h light–dark cycle as experienced by humans in day-to-day life (in contrast, circadian rhythms are internal processes regulated by circadian clocks, independent of external cues; establishing rhythms as circadian requires complex laboratory study protocols [eg, forced desynchrony or constant routine protocols], thus not all diurnal rhythms are confirmed to be true circadian rhythms, particularly in observational studies) |
| Entrainment                           | The process by which external cues, such as light (the strongest zeitgeber) or nutrient intake, synchronize the internal circadian clocks to the 24-h day–night cycle  |
| Glucocorticoid rhythms                | Daily cycles of glucocorticoid hormones, such as cortisol, regulated by the circadian system and important for stress response and metabolism  |
| Melatonin                             | Circadian hormone that marks the internal circadian phase and is a primary marker of the central circadian clock; secreted at night and suppressed by light; onset occurs ≈2 to 4 h before anticipated bedtime; evening DLMO is the gold standard measurement of internal circadian phase  |
| Nadir                                 | Characteristic of a rhythm: the lowest value (trough) of a rhythm or time when it occurs   |
| Peripheral circadian clocks           | Circadian cellular clocks found throughout the cells and tissues in the body, including cardiomyocytes   |
| Sleep regularity                      | Consistent sleep–wake schedule; sleeping at the same time every day  |
| Social jet lag                        | Timing of sleep varying substantially between days of the week, as if traveling across time zones  |
| Suprachiasmatic nucleus               | The primary circadian pacemaker in the hypothalamus; receives light signals through the retinal–hypothalamic tract and coordinates internal rhythms with the external environment  |
| Zeitgeber                             | A time-giving external cue, such as light or feeding, that synchronizes internal circadian clocks to the 24-h day–night cycle; from German for “time-giver”  |

DLMO indicates dim light melatonin onset.

central clock and to each other.<sup>5</sup> Other zeitgebers for central and peripheral clocks include timing of meals and exercise.<sup>4</sup> Alignment of these clocks is imperative for health; misalignment impairs cardiometabolic function (Figure).

Disruptions to circadian rhythms can be caused by disease; rotating or night shift work; mistimed sleep, meals, or exercise; or circadian rhythm sleep–wake disorders that present as advanced, delayed, or irregular rhythms, although directly measuring circadian phase or circadian disruption in the clinic or at home is difficult with current available tools.<sup>7</sup> Circadian rhythms are also influenced by one's chronotype, which refers to one's internal clock timing (eg, a morning person with an early or advanced internal rhythm, versus a night person with

a late or delayed rhythm). Circadian disruption can occur if chronotype does not align with behavior. For example, if an evening person must wake earlier than their circadian clock expects, they will be awake during their biologic night, which could disrupt circadian rhythms. Understanding circadian disruptors and their physiologic influence on cardiometabolic health could elucidate approaches to minimize detrimental consequences of circadian disruption.

This AHA scientific statement provides an overview of the associations between circadian biology and cardiometabolic health, emphasizing behavioral factors affecting circadian rhythms, and describes interventions to enhance circadian health that may improve cardiometabolic outcomes. Take-home pearls are summarized in Table 2.

## FACTORS THAT AFFECT THE CIRCADIAN SYSTEM

### Light Exposure

Light is the primary zeitgeber for synchronizing circadian rhythms.<sup>4</sup> Light exposure in the biologic morning advances the central clock (ie, timing becomes earlier), whereas light exposure in the biologic evening delays this clock. There are published recommendations for optimal daytime, evening, and nighttime indoor light exposure.<sup>8</sup> For instance, exposure to bright light in the morning, particularly natural sunlight, is essential for synchronizing circadian rhythms to the light–dark cycle, promoting alertness, and maintaining a healthy sleep–wake cycle.<sup>8</sup> Daytime light exposure, including bright indoor lighting that mimics natural daylight, should be maintained to support wakefulness and cognitive function.<sup>8</sup> Furthermore, recommendations warn against bright light exposure in the evening, especially short-wavelength (blue–green) light, as it can delay the central clock timing and disrupt the circadian rhythm.<sup>8,9</sup> Light at

night also suppresses melatonin secretion,<sup>9</sup> which feeds back to the suprachiasmatic nucleus and alters entrainment between internal and external rhythms. As such, exposure to light at night from electronic devices could adversely affect the central circadian clock while making it more difficult to fall asleep.<sup>8</sup>

### Sleep–Wake Patterns

Sleep–wake patterns are partially controlled by the circadian system,<sup>10</sup> but changes in sleep timing can also affect the circadian system. These effects are primarily mediated by light exposure and its influence on the central circadian clock.<sup>11,12</sup> Advancing the timing of sleep (ie, earlier bedtime or waketime) results in a phase advance due to reduced evening light exposure and increased morning light exposure.<sup>13</sup> Delaying the timing of sleep (ie, later bedtime or waketime) results in a phase delay due to increased evening light exposure and decreased morning light exposure. Apart from alterations in light exposure, direct effects of sleep–wake times on the central circadian clock have not been consistently observed.<sup>11</sup> However, substantial day-to-day variability in sleep duration and timing could cause circadian disruption as it involves inconsistent timing of exposure to zeitgebers such as light, food, and exercise. Therefore, high day-to-day variability in sleep–wake timing, as seen in shift work or jet lag, could lead to substantial circadian disruption.

### Timing of Food Intake

Timing of food intake or meals, a key aspect of chrononutrition, may act as a zeitgeber for central and peripheral circadian clocks. Early work in animal models that restricted the time of food availability suggested that the circadian system could entrain to food intake.<sup>14,15</sup> Moreover, appetite-regulating hormones (eg, ghrelin) and metabolites derived from nutrient intake (eg, glucose or fatty acids) have been proposed as zeitgebers in peripheral clocks of organs involved in metabolism.<sup>4</sup> If meal timing is not aligned with the central clock, then internal circadian disruption could occur. Indeed, experimental studies in humans that shifted meal timing revealed no change in the timing of rhythms controlled by the central clock (eg, cortisol, melatonin), but rhythms reflecting peripheral clocks, including those of organs and tissues involved in metabolic processes (eg, glucose, leptin), were shifted.<sup>14</sup>

Burgeoning epidemiologic evidence connects irregular eating patterns, late-night eating, and prolonged eating windows with greater risk of obesity, T2D, and cardiovascular disease (CVD),<sup>16</sup> suggesting that misaligning meal times with the body's circadian rhythms negatively affects cardiometabolic health. Eating earlier in the day, which may align with the body's natural circadian rhythm, has been associated with better cardiometabolic

**Table 2. Take-Home Pearls**

|   |   |
|---|---|
| 1 | Circadian disruption has substantial effects on cardiometabolic health  |
| 2 | Sleep timing regularity is as important as sleep duration   |
| 3 | Light exposure timing is a therapeutic tool, but its effect depends on its timing relative to a person's internal clock                                       |
| 4 | Meal timing affects metabolic health beyond caloric content and later timing tends to be associated with worse outcomes                                       |
| 5 | Physical activity timing to increase circadian alignment (rhythmicity) may enhance circadian health   |
| 6 | Individual chronotype should be considered in guiding the timing of interventions or treatment  |
| 7 | Optimizing circadian rhythms through behavioral modifications is a promising approach for cardiometabolic disease prevention that warrants more investigation |

health.<sup>16</sup> Although there is some evidence that meal timing can influence circadian rhythmicity, there is a need to address limitations in the field, such as heterogeneity in definitions and measurement of meal timing.<sup>14</sup> It is also important to understand the modifiable determinants of temporal eating patterns, investigate the role of chrononutrition in the context of other dimensions of diet (eg, quantity, quality, food security) in achieving circadian and cardiometabolic health, understand the role of individual variability in response to chrononutrition, and elucidate underlying physiologic mechanisms through which meal timing affects the circadian system and cardiometabolic pathways.<sup>16</sup>

## Exercise

Exercise influences the circadian system and has been used to accelerate entrainment to simulated shift-work conditions.<sup>17</sup> Single or multiple bouts of exercise produce phase shifts based on their timing. In a laboratory-controlled study that assessed the phase-shifting effects of exercise, 60-minute bouts of moderate-intensity exercise were performed for 3 consecutive days at one of 8 times that were equally distributed across the 24-hour day and assessed relative to the onset of urinary excretion of aMT6s (6-sulphatoxymelatonin), a melatonin metabolite and circadian phase marker. Exercise performed at the equivalent of 7:00 AM (ie,  $\approx 7.7$  or 9.0 hours after mean aMT6s onset for younger and older adults, respectively) or between the equivalent of 1:00 PM and 4:00 PM resulted in phase advances of the central circadian clock; equivalent exercise performed between the equivalent of 7:00 PM and 10:00 PM led to phase delays.<sup>18</sup> The magnitude of phase shift effect of exercise may depend on chronotype.<sup>19</sup> In young adults, both morning and evening exercise led to phase advances in late chronotypes, but in early chronotypes, morning exercise led to a phase advance whereas evening exercise led to a phase delay.<sup>19</sup> Phase-shifting effects of exercise are generally similar between men and women<sup>18,19</sup> and age groups.<sup>18</sup> Exercise effects on circadian rhythms are less robust than bright light exposure of similar duration.<sup>20</sup>

In addition to its impact on the central circadian clock, exercise helps synchronize peripheral clocks in cells throughout the body. Exercise influences the phase of circadian clock genes in skeletal muscle depending on exercise timing and downstream transcription and metabolic responses.<sup>21</sup> The effect of exercise on skeletal muscle clocks is particularly relevant in the context of cardiometabolic risk, as skeletal muscle plays a key role in metabolism. Much remains to be researched in this area, including the relative impact of exercise on central versus peripheral clocks, whether exercise exerts additive effects with other time cues (eg, bright light, food intake timing), and whether there is a dose-response effect based on exercise duration.

## ASSOCIATIONS WITH CARDIOMETABOLIC HEALTH

### Obesity and Weight Gain

Circadian rhythms regulate metabolism, energy expenditure, and appetite, which are key for healthy weight maintenance, and circadian disruption has been associated with weight gain and obesity.<sup>22</sup> Epidemiologic studies demonstrated that rotating and night shift work is associated with higher body mass index, obesity risk, and central adiposity.<sup>23</sup> Social jet lag (ie, variation in sleep timing between work or school days and free days) was associated with 23% higher odds of overweight or obesity in a meta-analysis.<sup>24</sup> Higher day-to-day variability in sleep duration and sleep onset timing has also been linked to obesity risk; a 1-hour increase in variability in sleep onset timing was associated with 25% higher odds of central obesity.<sup>25</sup> Inappropriate timing of food intake, such as during the biologic night, is another source of circadian disruption associated with increased body weight.<sup>26</sup> Irregular meal timing has also been associated with higher body mass index and waist circumference.<sup>27</sup> Together, these studies demonstrate that factors known to induce circadian disruption are risk factors for weight gain and obesity. Overall, circadian disruption exacerbates metabolic dysregulation resulting in increased risk for weight gain. The proposed mechanisms include altered appetite-regulating hormones, reduced energy expenditure, increased energy intake, glucose dysregulation, and alterations in metabolic rate.<sup>22</sup>

### Type 2 Diabetes

Greater rhythmicity of lifestyle behaviors is associated with lower risk of glycemic dysregulation and T2D.<sup>16,25,28</sup> Less robust rest-activity rhythms in free-living settings are associated with 2- to 3-fold higher T2D risk, greater odds of impaired glucose tolerance and insulin resistance, and higher fasting glucose, glycated hemoglobin, and insulin levels.<sup>28</sup> The timing and regularity of sleep also play a role in diabetes pathogenesis, with social jet lag and greater day-to-day variability in sleep duration and timing emerging as risk factors for glycemic dysregulation and T2D.<sup>25,28</sup> These associations persisted across various populations and sociodemographic groups, and were independent of known T2D risk factors. Night and rotating shift work are associated with later sleep timing, irregular sleep patterns, and a mismatch between chronotype and timing of work and sleep, leading to circadian disruption and predisposition to T2D, particularly when coupled with other unhealthy lifestyle behaviors.<sup>28</sup> Light exposure at night also contributed to incident T2D and gestational diabetes in Asian cohort studies.<sup>16</sup>

Later meal timing and greater extent of nighttime eating have also been linked to T2D risk, although there is limited evidence from observational data.<sup>16</sup>

Time-restricted eating (TRE), where food intake is limited to a specific window during the day (eg, 8–10 hours), is associated with better glucose tolerance and insulin sensitivity,<sup>16</sup> mostly when TRE confines nutrient intake to appropriate times (eg, daytime). Eating earlier in the day may also have beneficial effects. In a prospective cohort, eating the first meal after 9:00 AM versus before 8:00 AM or eating the last meal after 9:00 PM versus before 8:00 PM was associated with 59% and 28% higher T2D risk, respectively.<sup>29</sup> Eating breakfast before 8:00 AM coupled with an overnight fast >13 hours was associated with 53% lower risk.<sup>29</sup> However, these were external clock times, and meal timing relative to the body's internal clock or chronotype should be considered. Emerging evidence also suggests that greater day-to-day variability in eating timing and extent of evening caloric intake is associated with increases in HbA1c over time, predisposing to T2D.<sup>27</sup>

## Hypertension

BP typically increases rapidly in the morning ("morning surge"), peaks in the afternoon, and decreases overnight ("dipping").<sup>2</sup> Normal dipping is defined as a decrease in systolic BP of  $\geq 10\%$  during sleep compared with wake-time; a  $< 10\%$  decrease in systolic BP is considered nondipping.<sup>2</sup> A nondipping pattern is associated with an increased risk of CVD events (15%) and mortality (22%), with higher risk noted in patients with hypertension (25% for CVD events and 30% for mortality).<sup>30</sup> Night-time (sleep) hypertension is also associated with adverse cardiovascular outcomes.<sup>31</sup> Both conditions are common, with an estimated prevalence of nondipping pattern of 25% to 64% and nighttime hypertension of 27% to 40%.<sup>2,31</sup>

Circadian disruption affects BP regulation and hypertension risk. Shift work increases systolic and diastolic BP and hypertension risk.<sup>31</sup> Meal timing may also affect BP control, as early TRE and earlier and more regular temporal eating patterns have been linked to lower BP.<sup>16</sup> In addition, the circadian rhythm of BP is disrupted in patients with chronic kidney disease,<sup>32</sup> which suggests that circadian disruption may be particularly relevant to cardiovascular–kidney–metabolic health, which is associated with cardiovascular disease incidence and mortality risk.<sup>33</sup> Several of the CLOCK (circadian locomotor output cycles kaput) genes have been shown to play a crucial role in BP regulation (see reference<sup>6</sup> for a review).

Some antihypertensive medications (eg,  $\beta$ -adrenergic blockers) are known to suppress endogenous melatonin<sup>34</sup> and melatonin supplementation may improve sleep in these patients.<sup>35</sup> Research in chronotherapy involving administration of antihypertensive medications at bedtime has generated substantial interest but yielded mixed results. Recent trials examining evening versus morning BP medication administration on a composite outcome

of death or hospitalization for heart failure, stroke, or acute coronary syndrome demonstrated no benefit or harm.<sup>36,37</sup> As such, the 2024 European Society of Cardiology Hypertension Guidelines recommend administering medications at times that are convenient for the patient to enhance adherence.<sup>38</sup> However, this does not take into account specific patient populations that may benefit from timed therapy, such as those with nondipping hypertension and shift workers. Furthermore, consideration of an individual's chronotype may improve chronotherapy approaches. Overall, disruption of the circadian rhythm of BP is associated with elevated BP, hypertension, and CVD risk, but additional research is needed to understand whether maximizing circadian rhythmicity through nonpharmacologic interventions improves BP regulation and reduces cardiometabolic risk.

## Cardiovascular Disease

Circadian misalignment from rotating and night shift work is an established CVD risk factor. A meta-analysis of observational studies demonstrated that shift workers have 17% higher CVD risk, including 26% higher coronary heart disease morbidity risk and 20% higher CVD mortality risk for every additional 5 years of exposure.<sup>39</sup> In the general population, rest–activity rhythms indicative of greater circadian rhythmicity were associated with up to 62% lower prevalent CVD, whereas more fragmented rhythms and a later and less restful sleep period were associated with greater CVD odds, with evidence of a dose-response association.<sup>40</sup> Sleep irregularity, in particular, has emerged as an important modifiable CVD risk factor; data from MESA (Multi-Ethnic Study of Atherosclerosis) indicated that greater day-to-day variability in sleep duration and timing was related to a >2-fold higher CVD risk.<sup>41</sup>

In terms of chrononutrition metrics, although numerous studies have linked meal timing to CVD risk factors, there is a dearth of population studies on CVD outcomes.<sup>16</sup> In a prospective cohort, every 1-hour delay in timing of the first meal was associated with 6% higher overall CVD risk and a 1-hour delay in the timing of the last meal was associated with an 8% increased risk of cerebrovascular disease.<sup>42</sup> Beyond behavioral rhythms, exposure to artificial light at night is associated with up to 34% higher risk of CVD and stroke, although this evidence is primarily geographically restricted to Asian cohort studies.<sup>29,43,44</sup>

## IMPLICATIONS FOR EQUITABLE HEALTH

Circadian misalignment can exacerbate cardiometabolic health disparities, disproportionately affecting individuals in low-resource settings or those working nontraditional schedules, such as shift workers. People from underrepresented racial or ethnic groups are more likely

to experience social or environmental stressors, such as rotating shift work or light pollution, that can disrupt circadian rhythms.<sup>45</sup> For example, individuals from socioeconomically disadvantaged populations are more likely to engage in shift work or hold multiple jobs with irregular hours, which increases susceptibility to misalignment and its associated cardiometabolic risks. Living in areas with limited access to healthy foods and green or walkable spaces as well as light pollution at night can compound the effects of circadian misalignment on cardiometabolic health. This disproportionate exposure is hypothesized to contribute to health inequities. Black adults and people with secondary hypertension have a higher prevalence of nondipping BP,<sup>2</sup> so interventions focused on improving circadian health may be particularly relevant and useful for these populations. Multilevel interventions and policy changes are needed that promote education on proper timing and regularity of sleep–wake cycles and meal schedules and facilitate improvements in, for instance, workplace and neighborhood environments. For example, later school start times are associated with improved student outcomes, such as reduced suspensions and higher grades, among students from socioeconomically disadvantaged populations.<sup>46</sup> These efforts are essential to mitigating the disproportionate burden of circadian misalignment on populations experiencing disparities in cardiometabolic health.

## INTERVENTIONS TO IMPROVE CIRCADIAN HEALTH

Interventions that focus on the timing of the therapy (ie, chronotherapy) have the potential to improve circadian health and potentially cardiometabolic diseases. Several such interventions are discussed in the following.

### Sleep Regularity and Melatonin Administration

Given the role of the central clock in orchestrating peripheral clocks for optimal cardiometabolic health, strategies to maintain alignment of the central clock to the external world along with alignment of peripheral clocks to the central clock are needed. The timing and regularity of sleep are relevant for the maintenance of proper alignment and can be achieved through behavioral strategies, such as adopting regular bedtimes and waketimes. However, despite increasing awareness of associations between irregular sleep timing and cardiometabolic risk,<sup>47,48</sup> little is known about the health effects of stabilizing sleep on core clock genes and peripheral rhythms in humans. Although cardiometabolic risk factors may reflect peripheral desynchrony, few studies have evaluated the impact of regular sleep timing on cardiometabolic health. One study noted improvements in weight and body composition in women who reduced their bedtime variability over

a 6-week period compared with a group who did not change or increased their bedtime variability.<sup>49</sup>

Melatonin is a key circadian hormone that signals to the central clock and influences its entrainment. Exogenous melatonin is particularly useful for blind individuals unable to entrain to the natural light–dark cycles.<sup>50</sup> In sighted individuals, appropriately timed melatonin administration can shift the central clock.<sup>50</sup> Morning melatonin administration delays circadian rhythms; administration in the evening leads to advanced circadian rhythms.<sup>50</sup> The dose used for shifting the central clock is typically  $\leq 1$  mg of immediate-release formulations and is taken  $\approx 2$  to 6 hours before bedtime if advancing is desired.<sup>51</sup> However, effects of melatonin supplementation on cardiometabolic health remain poorly understood. Previous research has shown that melatonin increases insulin resistance<sup>52</sup> and is associated with greater glycemic variability in patients with T2D.<sup>53</sup> Furthermore, in the United States, melatonin is considered a supplement, and is therefore not regulated by the Food and Drug Administration as a drug. Studies have demonstrated that the amount of melatonin contained in supplements is highly variable.<sup>54</sup> Moreover, although melatonin supplementation is commonly used to promote sleep in children, long-term safety and effects on development, endocrine function, and circadian regulation remain insufficiently studied and are not well-understood. Therefore, caution is warranted when considering melatonin supplementation.

### Light Exposure

As described, light is a primary zeitgeber; therefore, appropriately timed light exposure can be an effective intervention for shifting circadian rhythms.<sup>50,55</sup> However, the effect of light exposure will depend on the person's internal clock timing<sup>55</sup>; therefore, assessing their internal circadian phase is important for timing light exposure. Light exposure interventions have been shown to improve mood, energy levels, and sleep.<sup>56–58</sup> Traditional recommendations suggest that a large dose of bright light is required for this effect, with  $\approx 10\,000$  lux (full daylight levels) being the recommended dose (for comparison, most office lighting is 300 to 500 lux). More recently, recommendations have accommodated lower intensities, especially if that light is enriched with short-wavelength (eg, blue–green) light, necessitating less light stimulation overall.<sup>59,60</sup> The timing of light exposure is important and recommendations generally suggest obtaining sufficient bright light (especially in the blue–green spectrum) starting early in the day and avoiding light, including light-emitting devices, in the evening before bedtime and during the night. Even low levels of light (eg, 100 lux) at night can suppress melatonin and delay the clock.<sup>9</sup> In addition, blocking light in the blue–green spectrum (eg, by using amber or red-tinted glasses or bulbs) may be helpful in the evening to reduce the degree to which

environmental light alters rhythms.<sup>61,62</sup> Several studies have examined the effects of light interventions on cardiometabolic outcomes, and found that morning light exposure is associated with lower body fat, body mass, and appetite.<sup>63</sup>

In clinical settings, irregular light exposure, as well as meal timing and activity patterns, are likely often overlooked by health care clinicians, despite its importance to patient health. Addressing these factors is central to circadian medicine, and guidelines emphasize its essential integration into critical cardiac care.

## Time-Restricted Eating

Because meal timing is a zeitgeber for circadian rhythms, TRE patterns could provide a strategy to maintain alignment of peripheral clocks to the central clock. Studies in rodent models show that feeding during the inactive period leads to greater weight gain despite similar food intake as mice fed during their active period.<sup>64</sup> One experimental study in humans found that TRE altered clock gene expression.<sup>65</sup> Meta-analyses and reviews that combined studies of TRE ranging from 4 to 12 hours observed improvements in body weight, adiposity, glucose level, total cholesterol level, and insulin resistance.<sup>65,66</sup> When analyses were restricted to studies that used an 8-hour eating window, TRE was associated with reductions in weight, fat mass, body mass index, systolic BP, and total cholesterol, but not in waist circumference, glycemic outcomes, or other lipid measures.<sup>66</sup> Furthermore, some evidence suggests that eating larger meals late in the day is associated with weight gain<sup>67</sup> and that TRE earlier in the day may have more beneficial cardiometabolic effects than later timing.<sup>68</sup> More studies are needed to evaluate optimal duration and timing of the eating window and meals on sleep and cardiometabolic health.

## Timed Physical Activity

Emerging research suggests that not only the amount but also the timing of exercise may be important for cardiometabolic health.<sup>69</sup> Exercise itself acts as a zeitgeber,<sup>18</sup> and many physiologic functions it affects (eg, BP, respiratory control, core body temperature) are also regulated by the circadian system. Furthermore, the response to exercise may vary by time of day, because muscle strength, endurance, and performance also vary, with peaks in the late afternoon/early evening.<sup>70</sup> Thus, exercise timing may influence health through direct effects on the central or peripheral circadian system or its downstream physiologic processes.

Observational studies have yielded inconsistent findings on the impact of exercise timing on cardiometabolic outcomes (eg, BP, HbA1c, triglycerides), with some favoring morning exercise, others supporting afternoon/evening activity, and some showing no difference.<sup>71</sup>

Experimental trials also provide mixed evidence. A systematic review found little support for timing-dependent health benefits.<sup>72</sup> However, a meta-analysis suggested better glycemic control and triglyceride reduction with afternoon/evening exercise, whereas another review suggested that morning exercise may optimize weight loss.<sup>73</sup> Overall, the quality of evidence on this topic remains low,<sup>71,72</sup> and future research needs to better account for factors such as medication use, prandial state, sex, chronotype, and timing of assessments, and should include pediatric through older adult populations.<sup>69</sup>

Exercise may also influence circadian health through its effects on sleep. Physical activity generally improves sleep regardless of its timing,<sup>74</sup> but vigorous exercise within an hour of bedtime may reduce sleep efficiency for some. Moderate to vigorous activity can enhance circadian rhythmicity.<sup>75</sup> The timing of physical activity could potentially benefit those with circadian misalignment (eg, shift workers, older adults, individuals with circadian rhythm sleep disorders).<sup>18</sup> Timed physical activity is a nonpharmacologic strategy that can improve circadian health by optimizing sleep quality, enhancing daytime alertness, and supporting cardiometabolic outcomes.

## SUMMARY AND FUTURE DIRECTIONS

The circadian system plays a crucial role in maintaining health, including cardiovascular and metabolic function, and optimal health relies on robust circadian rhythmicity. Circadian rhythm timing is determined by several cues (zeitgebers), with light being the primary factor to entrain the central clock. Modifiable behaviors, including the timing and regularity of sleep (which could act through light exposure), meal timing, and timing of physical activity, also have the potential to alter central and peripheral clocks. Disrupting circadian rhythms through shift work, irregular sleep timing, or inappropriate timing of meals, sleep, light exposure, or exercise has been linked to adverse cardiometabolic outcomes, including obesity, T2D, hypertension, and cerebrovascular diseases. These zeitgebers are potential targets of interventions aimed at improving circadian health and, ultimately, cardiometabolic health. However, additional research is required to establish causation and elucidate pragmatic and effective interventions. The timing of factors relevant to circadian health (eg, light exposure, meals, physical activity) needs to be considered relative to a person's internal clock and chronotype, beyond external clock time.

Evidence to establish an unequivocal link between circadian disruption and cardiometabolic disease is required, as is research to identify whether optimizing circadian rhythmicity can improve cardiometabolic health. Most existing human studies involved small sample sizes and controlled experimental designs. A challenge to the field is the availability of validated measures of central and peripheral circadian rhythmicity<sup>7</sup> that can be used in

large population-based prospective studies to evaluate associations with the development of chronic diseases across the life course. Assessing true circadian rhythms requires complex experimental studies that are feasible only in small-scale, tightly controlled experiments. Furthermore, physicians often rely on indirect markers, such as patient-reported bedtime, as practical but imprecise proxies for circadian timing. With advances in metabolomics, wearable technologies, and artificial intelligence, alternative methods may be developed to assess circadian rhythms, such as 24-hour patterns in skin temperature and heart rate.

Interventions to improve circadian health may have a beneficial effect on cardiometabolic health. Sleep timing and its regularity can be improved through modifying the zeitgebers. Properly timed light exposure can help maintain appropriate endogenous melatonin production and secretion. Appropriately timed eating patterns and physical activity are also potential intervention targets that can improve circadian health through effects on peripheral clocks, core body temperature, and hormone regulation. Research is needed to determine the efficacy, effectiveness, and implementation of circadian health interventions in different populations and settings and their role in advancing health for all.

Researchers, clinicians, and the public must appreciate the importance of circadian rhythms and the role of modifiable behaviors that optimize or disrupt endogenous rhythms for overall health and well-being. Circadian health is related to, but separate from, sleep health; it helps regulate many physiologic functions beyond sleep, including those important for cardiometabolic health. This scientific statement is intended to stimulate innovative

research in this area to advance our understanding of how best to support cardiometabolic health and enhance CVD prevention approaches.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 8, 2025, and the American Heart Association Executive Committee on September 30, 2025. A copy of the document is available at <https://professional.heart.org/statements> by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email [Meredith.Edelman@wolterskluwer.com](mailto:Meredith.Edelman@wolterskluwer.com)

The American Heart Association requests that this document be cited as follows: Knutson KL, Dixon DD, Grandner MA, Jackson CL, Kline CE, Maher L, Makarem N, Martino TA, St-Onge M-P, Johnson DA; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifelong Congenital Heart Disease and Heart Health in the Young. Role of circadian health in cardiometabolic health and disease risk: a scientific statement from the American Heart Association. *Circulation*. 2025;152:e000000000001388. doi: 10.1161/CIR.0000000000001388

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <https://professional.heart.org/statements>. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development"

Permissions: Multiple copies, modification, alteration, enhancement, and distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the "Copyright Permissions Request Form" appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).

Sources of Funding

This work was, in part, funded by the Intramural Program at the NIH, National Institute of Environmental Health Sciences (Z1AES103325; C.L. Jackson).

Disclosures

Writing Group Disclosures

| Writing group member | Employment  | Research grant                              | Other research support | Speakers' bureau/honoraria | Expert witness | Ownership interest | Consultant/advisory board                             | Other |
|----------------------|---|---|------------------------|----------------------------|----------------|--------------------|---|-------|
| Kristen L. Knutson   | Northwestern University Feinberg School of Medicine | None  | None                   | None                       | None           | None               | None  | None  |
| Dayna A. Johnson     | Emory University                                    | None  | None                   | None                       | None           | None               | None  | None  |
| Debra D. Dixon       | Vanderbilt University Medical Center                | AHRQ/PCORI†                                 | None                   | None                       | None           | None               | None  | None  |
| Michael A. Grandner  | University of Arizona College of Medicine           | Harmony Biosciences (PI of research grant)† | None                   | None                       | None           | None               | Googlet; Natrol†; WNDR Health†; Smartypants Vitamins† | None  |
| Chandra L. Jackson   | National Institutes of Health                       | None  | None                   | None                       | None           | None               | None  | None  |
| Christopher E. Kline | University of Pittsburgh                            | None  | None                   | None                       | None           | None               | None  | None  |
| Lisa Maher           | Self-employed                                       | None  | None                   | None                       | None           | None               | None  | None  |

(Continued)

## Writing Group Disclosures Continued

| Writing group member | Employment   | Research grant   | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other   |
|----------------------|--|--|------------------------|-----------------------------|----------------|--------------------|----------------------------|---|
| Nour Makarem         | Columbia University Irving Medical Center, Mailman School of Public Health | NIH (PI of NIH grants) <sup>†</sup> ; American Heart Association (PI of AHA grants) <sup>†</sup> | None                   | None                        | None           | None               | None                       | Columbia University Irving Medical Center, Mailman School of Public Health (assistant professor) <sup>†</sup> |
| Tami A. Martino      | University of Guelph Centre for Cardiovascular Investigations (Canada)     | None   | None                   | None                        | None           | None               | None                       | None  |
| Marie-Pierre St-Onge | Columbia University  | None   | None                   | None                        | None           | None               | None                       | None  |

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives ≥\$5000 during any 12-month period, or ≥5% of the person's gross income; or (b) the person owns ≥5% of the voting stock or share of the entity, or owns ≥\$5000 of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## Reviewer Disclosures

| Reviewer             | Employment                                | Research grant   | Other research support | Speakers' bureau/ honoraria | Expert witness                | Ownership interest                             | Consultant/ advisory board                     | Other |
|----------------------|---|--|------------------------|-----------------------------|-------------------------------|--|--|-------|
| Nicole P. Bowles     | Oregon Health & Science University        | None   | None                   | None                        | McGillivray Steele Elkin LLP* | None   | None   | None  |
| Michelle L. Gumz     | University of Florida                     | None   | None                   | None                        | None                          | None   | None   | None  |
| Julie Pendergast     | University of Kentucky                    | NIH (PI of an R01 grant that investigates the role of estrogens in regulating circadian rhythms underlying metabolic risk in female mice and postmenopausal women; the topic is relevant to this article, but no collaboration with the authors of this article exists) <sup>†</sup>               | None                   | None                        | None                          | None   | None   | None  |
| Michael H. Smolensky | University of Texas Health Science Center | NIH Division of Minority Health (assessment of the clinical utility of data derived from 48-hour blood pressure monitoring in combination with those derived from a unique home blood pressure monitoring device on progression of chronic kidney disease to kidney failure and need of dialysis)* | None                   | None                        | None                          | Circadian Ambulatory Technology & Diagnostics* | Circadian Ambulatory Technology & Diagnostics* | None  |
| S. Justin Thomas     | University of Alabama at Birmingham       | NIH (PI of R01HL167230) <sup>†</sup>   | None                   | None                        | None                          | None   | None   | None  |

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives ≥\$5000 during any 12-month period, or ≥5% of the person's gross income; or (b) the person owns ≥5% of the voting stock or share of the entity, or owns ≥\$5000 of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## REFERENCES

- Crowthers R, Thi Mong Nguyen T, Martinez D. Circadian disruptions and their role in the development of hypertension. *Front Neurosci*. 2024;18:1433512. doi: 10.3389/fnins.2024.1433512
- Huart J, Persu A, Lengele JP, Krzesinski JM, Jouret F, Stergiou GS. Pathophysiology of the nondipping blood pressure pattern. *Hypertension*. 2023;80:719–729. doi: 10.1161/HYPERTENSIONAHA.122.19996
- Chellappa SL, Vujovic N, Williams JS, Scheer F. Impact of circadian disruption on cardiovascular function and disease. *Trends Endocrinol Metab*. 2019;30:767–779. doi: 10.1016/j.tem.2019.07.008
- Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol*. 2010;72:517–549. doi: 10.1146/annurev-physiol-021909-135821
- Koronowski KB, Sassone-Corsi P. Communicating clocks shape circadian homeostasis. *Science*. 2021;371:eabd0951. doi: 10.1126/science.abd0951
- Costello HM, Gumz ML. Circadian rhythm, clock genes, and hypertension: recent advances in hypertension. *Hypertension*. 2021;78:1185–1196. doi: 10.1161/HYPERTENSIONAHA.121.14519
- Duffy JF, Abbott SM, Burgess HJ, Crowley SJ, Emens JS, Epstein LJ, Gamble KL, Hasler BP, Kristo DA, Malkani RG, et al. Workshop report:

- circadian rhythm sleep–wake disorders: gaps and opportunities. *Sleep*. 2021;44:zsaa281. doi: 10.1093/sleep/zsaa281
8. Brown TM, Brainard GC, Cajochen C, Czeisler CA, Hanifin JP, Lockley SW, Lucas RJ, Munch M, O'Hagan JB, Peirson SN, et al. Recommendations for daytime, evening, and nighttime indoor light exposure to best support physiology, sleep, and wakefulness in healthy adults. *PLoS Biol*. 2022;20:e3001571. doi: 10.1371/journal.pbio.3001571
  9. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol*. 2000;526:695–702. doi: 10.1111/j.1469-7793.2000.00695.x
  10. Dijk DJ, Archer SN. Light, sleep, and circadian rhythms: together again. *PLoS Biol*. 2009;7:e1000145. doi: 10.1371/journal.pbio.1000145
  11. Appleman K, Figueiro MG, Rea MS. Controlling light–dark exposure patterns rather than sleep schedules determines circadian phase. *Sleep Med*. 2013;14:456–461. doi: 10.1016/j.sleep.2012.12.011
  12. Duffy JF, Kronauer RE, Czeisler CA. Phase-shifting human rhythms: influence of sleep timing, social contact, and light exposure. *J Physiol*. 1996;495:289–297. doi: 10.1113/jphysiol.1996.sp021593
  13. Sletten TL, Vincenzi S, Redman JR, Lockley SW, Rajaratnam SM. Timing of sleep and its relationship with the endogenous melatonin rhythm. *Front Neurol*. 2010;1:137. doi: 10.3389/fneur.2010.00137
  14. Lewis P, Oster H, Korf HW, Foster RG, Erren TC. Food as a circadian time cue: evidence from human studies. *Nat Rev Endocrinol*. 2020;16:213–223. doi: 10.1038/s41574-020-0318-z
  15. Challet E, Mendoza J. Metabolic and reward feeding synchronises the rhythmic brain. *Cell Tissue Res*. 2010;341:1–11. doi: 10.1007/s00441-010-1001-9
  16. Raji OE, Kyeremah EB, Sears DD, St-Onge M-P, Makarem N. Chrononutrition and cardiometabolic health: an overview of epidemiological evidence and key future research directions. *Nutrients*. 2024;16:2332. doi: 10.3390/nu16142332
  17. Yamanaka Y, Hashimoto S, Masubuchi S, Natsubori A, Nishide SY, Honma S, Honma K. Differential regulation of circadian melatonin rhythm and sleep–wake cycle by bright lights and nonphotic time cues in humans. *Am J Physiol Regul Integr Comp Physiol*. 2014;307:R546–R557. doi: 10.1152/ajpregu.00087.2014
  18. Youngstedt SD, Elliott JA, Kripke DF. Human circadian phase-response curves for exercise. *J Physiol*. 2019;597:2253–2268. doi: 10.1113/JP276943
  19. Thomas JM, Kern PA, Bush HM, McQuerry KJ, Black WS, Clasey JL, Pendergast JS. Circadian rhythm phase shifts caused by timed exercise vary with chronotype. *JCI Insight*. 2020;5:e134270. doi: 10.1172/jci.insight.134270
  20. Youngstedt SD, Kline CE, Elliott JA, Zielinski MR, Devlin TM, Moore TA. Circadian phase-shifting effects of bright light, exercise, and bright light + exercise. *J Circadian Rhythms*. 2016;14:2. doi: 10.5334/jcr.137
  21. Martin RA, Esser KA. Time for exercise? Exercise and its influence on the skeletal muscle clock. *J Biol Rhythms*. 2022;37:579–592. doi: 10.1177/07487304221122662
  22. Chaput JP, McHill AW, Cox KC, Broussard JL, Dutil C, da Costa BGG, Sampasa-Kanyinga H, Wright KP Jr. The role of insufficient sleep and circadian misalignment in obesity. *Nat Rev Endocrinol*. 2023;19:82–97. doi: 10.1038/s41574-022-00747-7
  23. Sun M, Feng W, Wang F, Li P, Li Z, Li M, Tse G, Vlaanderen J, Vermeulen R, Tse LA. Meta-analysis on shift work and risks of specific obesity types. *Obes Rev*. 2018;19:28–40. doi: 10.1111/obr.12621
  24. Arab A, Karimi E, Garaulet M, Scheer F. Social jetlag and obesity: a systematic review and meta-analysis. *Obes Rev*. 2024;25:e13664. doi: 10.1111/obr.13664
  25. Huang T, Redline S. Cross-sectional and prospective associations of actigraphy-assessed sleep regularity with metabolic abnormalities: the Multi-Ethnic Study of Atherosclerosis. *Diabetes Care*. 2019;42:1422–1429. doi: 10.2337/dc19-0596
  26. Davis R, Rogers M, Coates AM, Leung GKW, Bonham MP. The impact of meal timing on risk of weight gain and development of obesity: a review of the current evidence and opportunities for dietary intervention. *Curr Diab Rep*. 2022;22:147–155. doi: 10.1007/s11892-022-01457-0
  27. Makarem N, Sears DD, St-Onge M-P, Zuraikat FM, Gallo LC, Talavera GA, Castaneda SF, Lai Y, Aggarwal B. Variability in daily eating patterns and eating jetlag are associated with worsened cardiometabolic risk profiles in the American Heart Association Go Red for Women strategically focused research network. *J Am Heart Assoc*. 2021;10:e020204. doi: 10.1161/JAHA.121.020204
  28. Zuraikat FM, Makarem N, Redline S, Aggarwal B, Jelic S, St-Onge M-P. Sleep regularity and cardiometabolic health: is variability in sleep patterns a risk factor for excess adiposity and glycemic dysregulation? *Curr Diab Rep*. 2020;20:38. doi: 10.1007/s11892-020-01324-w
  29. Palomar-Cros A, Srour B, Andreeva VA, Fezeu LK, Bellicha A, Kesse-Guyot E, Hercberg S, Romaguera D, Kogevinas M, Touvier M. Associations of meal timing, number of eating occasions and night-time fasting duration with incidence of type 2 diabetes in the NutriNet-Sante cohort. *Int J Epidemiol*. 2023;52:1486–1497. doi: 10.1093/ije/dyad081
  30. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. *Hypertension*. 2011;57:3–10. doi: 10.1161/HYPERTENSIONAHA.109.133900
  31. Gumz ML, Shimbo D, Abdalla M, Balijepalli RC, Benedict C, Chen Y, Earnest DJ, Gamble KL, Garrison SR, Gong MC, et al. Toward precision medicine: circadian rhythm of blood pressure and chronotherapy for hypertension: 2021 NHLBI workshop report. *Hypertension*. 2023;80:503–522. doi: 10.1161/HYPERTENSIONAHA.122.19372
  32. Mohandas R, Douma LG, Scindia Y, Gumz ML. Circadian rhythms and renal pathophysiology. *J Clin Invest*. 2022;132:e148277. doi: 10.1172/JCI148277
  33. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM, Carnethon MR, et al; American Heart Association. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. *Circulation*. 2023;148:1606–1635. doi: 10.1161/CIR.0000000000001184
  34. Stoschitzky K, Sakotnik A, Lercher P, Zweiker R, Maier R, Liebmann P, Lindner W. Influence of beta-blockers on melatonin release. *Eur J Clin Pharmacol*. 1999;55:111–115. doi: 10.1007/s002280050604
  35. Scheer FA, Morris CJ, Garcia JL, Smales C, Kelly EE, Marks J, Malhotra A, Shea SA. Repeated melatonin supplementation improves sleep in hypertensive patients treated with beta-blockers: a randomized controlled trial. *Sleep*. 2012;35:1395–1402. doi: 10.5665/sleep.2122
  36. Garrison SR, Youngson ERE, Perry DA, Campbell FN, Korownyk CS, Green LA, Kolber MR, Kirkwood JEM, Allan GM, Kraut RY, et al. Bedtime vs morning antihypertensive medications in frail older adults: the BedMed-Frail randomized clinical trial. *JAMA Netw Open*. 2025;8:e2513812. doi: 10.1001/jamanetworkopen.2025.13812
  37. Garrison SR, Bakal JA, Kolber MR, Korownyk CS, Green LA, Kirkwood JEM, McAlister FA, Padwal RS, Lewanczuk R, Hill MD, et al. Antihypertensive medication and cardiovascular events and death: the BedMed randomized clinical trial. *JAMA*. 2025;333:2061. doi: 10.1001/jama.2025.4390
  38. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, Christodorescu RM, Daskalopoulou SS, Ferro CJ, Gerds E, et al; ESC Scientific Document Group. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. 2024;45:3912–4018. doi: 10.1093/eurheartj/ehae178
  39. Torquati L, Mielke GI, Brown WJ, Kolbe-Alexander T. Shift work and the risk of cardiovascular disease: a systematic review and meta-analysis including dose-response relationship. *Scand J Work Environ Health*. 2018;44:229–238. doi: 10.5271/sjweh.3700
  40. Makarem N, German CA, Zhang Z, Diaz KM, Palta P, Duncan DT, Castro-Diehl C, Shechter A. Rest-activity rhythms are associated with prevalent cardiovascular disease, hypertension, obesity, and central adiposity in a nationally representative sample of US adults. *J Am Heart Assoc*. 2024;13:e032073. doi: 10.1161/JAHA.122.032073
  41. Huang T, Mariani S, Redline S. Sleep irregularity and risk of cardiovascular events: the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*. 2020;75:991–999. doi: 10.1016/j.jacc.2019.12.054
  42. Palomar-Cros A, Andreeva VA, Fezeu LK, Julia C, Bellicha A, Kesse-Guyot E, Hercberg S, Romaguera D, Kogevinas M, Touvier M, et al. Dietary circadian rhythms and cardiovascular disease risk in the prospective NutriNet-Sante cohort. *Nat Commun*. 2023;14:7899. doi: 10.1038/s41467-023-43444-3
  43. Hu X, Wang LB, Jalaludin B, Knibbs LD, Yim SHL, Lao XQ, Morawska L, Nie Z, Zhou Y, Hu LW, et al. Outdoor artificial light at night and incident cardiovascular disease in adults: a national cohort study across China. *Sci Total Environ*. 2024;918:170685. doi: 10.1016/j.scitotenv.2024.170685
  44. Wu Y, Shen P, Yang Z, Yu L, Xu L, Zhu Z, Li T, Luo D, Lin H, Shui L, et al. Outdoor light at night, air pollution, and risk of cerebrovascular disease: a cohort study in China. *Stroke*. 2024;55:990–998. doi: 10.1161/STROKEAHA.123.044904
  45. Johnson DA, Cheng P, Farr-Henderson M, Knutson K. Understanding the determinants of circadian health disparities and cardiovascular disease. *Chronobiol Int*. 2023;40:83–90. doi: 10.1080/07420528.2021.1966026

46. Bastian KC, Fuller SC. Answering the bell: high school start times and student academic outcomes. *Aera Open*. 2018;4: doi: 10.1177/2332858418812424
47. Chaput JP, Biswas RK, Ahmadi M, Cistulli PA, Sabag A, St-Onge M-P, Stamatakis E. Sleep irregularity and the incidence of type 2 diabetes: a device-based prospective study in adults. *Diabetes Care*. 2024;47:2139–2145. doi: 10.2337/dc24-1208
48. Full KM, Huang T, Shah NA, Allison MA, Michos ED, Duprez DA, Redline S, Lutsey PL. Sleep irregularity and subclinical markers of cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc*. 2023;12:e027361. doi: 10.1161/JAHA.122.027361
49. St-Onge M-P, Campbell A, Zuraikat F, Cheng B, Shah R, Berger JS, Sampogna RV, Jelic S. Impact of change in bedtime variability on body composition and inflammation: secondary findings from the Go Red for Women Strategically Focused Research Network. *Int J Obes (Lond)*. 2020;44:1803–1806. doi: 10.1038/s41366-020-0555-1
50. Skene DJ. Optimization of light and melatonin to phase-shift human circadian rhythms. *J Neuroendocrinol*. 2003;15:438–441. doi: 10.1046/j.1365-2826.2003.01006.x
51. Munday K, Benloucif S, Harsanyi K, Dubocovich ML, Zee PC. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. *Sleep*. 2005;28:1271–1278. doi: 10.1093/sleep/28.10.1271
52. Rubio-Sastre P, Scheer FA, Gomez-Abellan P, Madrid JA, Garaulet M. Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. *Sleep*. 2014;37:1715–1719. doi: 10.5665/sleep.4088
53. Martorina W, Tavares A. Glycemic variability in patients with type 2 diabetes mellitus (T2DM): the role of melatonin in a crossover, double-blind, placebo-controlled, randomized study. *Nutrients*. 2023;15:3523. doi: 10.3390/nu15163523
54. Pawar RS, Coppin JP, Khanna S, Parker CH. A survey of melatonin in dietary supplement products sold in the United States. *Drug Test Anal*. 2024;17:1176–1185. doi: 10.1002/dta.3823
55. St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW. Human phase response curve to a 1 h pulse of bright white light. *J Physiol*. 2012;590:3035–3045. doi: 10.1113/jphysiol.2012.227892
56. Bais B, Hoogendijk WJG, Lambregtse-van den Berg MP. Light therapy for mood disorders. *Handb Clin Neurol*. 2021;182:49–61. doi: 10.1016/B978-0-12-819973-2.00004-6
57. Culnan E, McCullough LM, Wyatt JK. Circadian rhythm sleep–wake phase disorders. *Neural Clin*. 2019;37:527–543. doi: 10.1016/j.ncl.2019.04.003
58. Chambe J, Reynaud E, Maruani J, Fraih E, Geoffroy PA, Bourgin P. Light therapy in insomnia disorder: a systematic review and meta-analysis. *J Sleep Res*. 2023;32:e13895. doi: 10.1111/jsr.13895
59. Vetter C, Phillips AJK, Silva A, Lockley SW, Glickman G. Light me up? Why, when, and how much light we need. *J Biol Rhythms*. 2019;34:573–575. doi: 10.1177/0748730419892111
60. Sun SY, Chen GH. Treatment of circadian rhythm sleep–wake disorders. *Curr Neuropsychopharmacol*. 2022;20:1022–1034. doi: 10.2174/1570159X19666210907122933
61. Mason BJ, Tubbs AS, Fernandez FX, Grandner MA. Spectrophotometric properties of commercially available blue blockers across multiple lighting conditions. *Chronobiol Int*. 2022;39:653–664. doi: 10.1080/07420528.2021.2021229
62. Burkhart K, Phelps JR. Amber lenses to block blue light and improve sleep: a randomized trial. *Chronobiol Int*. 2009;26:1602–1612. doi: 10.3109/07420520903523719
63. Ishihara A, Courville AB, Chen KY. The complex effects of light on metabolism in humans. *Nutrients*. 2023;15:1391. doi: 10.3390/nu15061391
64. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. Circadian timing of food intake contributes to weight gain. *Obesity (Silver Spring)*. 2009;17:2100–2102. doi: 10.1038/oby.2009.264
65. Lages M, Carmo-Silva S, Barros R, Guarino MP. Effects of time-restricted eating on body composition, biomarkers of metabolism, inflammation, circadian system and oxidative stress in overweight and obesity: an exploratory review. *Proc Nutr Soc*. 2024;1–10. doi: 10.1017/S002966512400747X
66. Liu L, Chen W, Wu D, Hu F. Metabolic efficacy of time-restricted eating in adults: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2022;107:3428–3441. doi: 10.1210/clinem/dgac570
67. Kinsey AW, Ormsbee MJ. The health impact of nighttime eating: old and new perspectives. *Nutrients*. 2015;7:2648–2662. doi: 10.3390/nu7042648
68. Jamshed H, Beyl RA, Della Manna DL, Yang ES, Ravussin E, Peterson CM. Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, aging, and autophagy in humans. *Nutrients*. 2019;11:1234. doi: 10.3390/nu11061234
69. Martinez-Montoro JI, Benitez-Porres J, Tinahones FJ, Ortega-Gomez A, Murri M. Effects of exercise timing on metabolic health. *Obes Rev*. 2023;24:e13599. doi: 10.1111/obr.13599
70. Noone J, Mucinski JM, DeLany JP, Sparks LM, Goodpaster BH. Understanding the variation in exercise responses to guide personalized physical activity prescriptions. *Cell Metab*. 2024;36:702–724. doi: 10.1016/j.cmet.2023.12.025
71. Janssen I, Campbell JE, Zahran S, Saunders TJ, Tomasone JR, Chaput JP. Timing of physical activity within the 24-hour day and its influence on health: a systematic review. *Health Promot Chronic Dis Prev Can*. 2022;42:129–138. doi: 10.24095/hpcdp.42.4.02
72. Bruggisser F, Knaier R, Roth R, Wang W, Qian H, Scheer F. Best time of day for strength and endurance training to improve health and performance? A systematic review with meta-analysis. *Sports Med Open*. 2023;9:34. doi: 10.1186/s40798-023-00577-5
73. Blankenship JM, Rosenberg RC, Rynders CA, Melanson EL, Catenacci VA, Creasy SA. Examining the role of exercise timing in weight management: a review. *Int J Sports Med*. 2021;42:967–978. doi: 10.1055/a-1485-1293
74. Kline CE, Hillman CH, Bloodgood Sheppard B, Tennant B, Conroy DE, Macko RF, Marquez DX, Petruzzello SJ, Powell KE, Erickson KI. Physical activity and sleep: an updated umbrella review of the 2018 Physical Activity Guidelines Advisory Committee report. *Sleep Med Rev*. 2021;58:101489. doi: 10.1016/j.smrv.2021.101489
75. Lewis P, Korf HW, Kuffer L, Gross JV, Erren TC. Exercise time cues (zeitgebers) for human circadian systems can foster health and improve performance: a systematic review. *BMJ Open Sport Exerc Med*. 2018;4:e000443. doi: 10.1136/bmjsem-2018-000443