HHS Public Access

Author manuscript

Prog Cardiovasc Dis. Author manuscript; available in PMC 2024 March 01.

Published in final edited form as:

Prog Cardiovasc Dis. 2023 ; 77: 70–77. doi:10.1016/j.pcad.2023.02.004.

Cardiovascular Disease and Lifestyle Choices: Spotlight on Circadian Rhythms and Sleep

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Abstract

The advent of electric lighting in the built environment has radically transformed the human experience of light and darkness, which is often insufficient to stimulate and synchronize the circadian system to the day-night cycle. The lack of circadian system entrainment leads to poor sleep and could be an important biophysical mechanism underlying increased incidence of certain types of diseases, including cardiovascular (CV) disease (CVD). This contribution proposes to carve out a niche for including daily exposures to light and darkness among lifestyle factors for reducing the risk and progression of CVD. The fundamental workings of the human circadian system and its primary outputs are described. The discussion then progresses to light's effects on the circadian system and its outputs, and how threats to circadian health pose risks for CV health. The contribution concludes with simple recommendations for incorporating regular, robust daily exposures in lifestyle adjustments to combat CVD risks and progression.

Keywords

Cardiovascular disease; circadian system; circadian rhythms disruption; light; melatonin

INTRODUCTION

Despite considerable gains in reducing mortality from cardiovascular (CV) disease (CVD) since the 1960s, the disease remains the leading cause of death of Americans (1). While the development of CVD is attributed to the interaction of individual genetic factors, broad-scale environmental inputs, and individual lifestyle choices, it is thought that environment and lifestyle are more dominant factors in the development of the disease (2).

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Conflict of interest: None.

CVD prevention should seek to promote optimal lifestyle choices, which include adherence to a healthy diet, regular physical activity, avoidance or cessation of smoking, moderation or abstinence from alcohol, and maintenance of a normal body weight (body mass index <25 kg/m^2) (3). The efficacy of these prevention guidelines is widely recognized, and though not immediately effective when adopted in middle age, they are believed to result in 35% reductions in CVD and 40% reductions in all-cause mortality within as few as 4 years (4).

In this contribution, we introduce a new modifiable lifestyle factor: daily exposure to consistent and robust light/dark patterns. Over 4 decades of research have established clear connections between the human circadian system and its constituent rhythms, the sleep/wake cycle, and general health and well-being (5, 6). Research has also shown that daily robust light/dark patterns are the main synchronizers of circadian rhythms to the local position on Earth. Lack of synchrony between the biological clock and the environment and between the biological clock and the body's various peripheral clocks can lead to circadian rhythms disruption. From this research has emerged a growing body of literature linking circadian rhythms disruption to a variety of chronic diseases (7–9), as shown in Figure 1. In the following sections we will draw links between circadian rhythm disturbances and CVD.

Research has firmly established that the CV system's various processes adhere to a rigorous 24-hour pattern (9–11), and that the coherent alignment of these processes relies on a highly regulated balance between the autonomous nervous system's parasympathetic and sympathetic domains (8). Also involved are the contributions of various exogenous environmental, social, and behavioral factors (see Lifestyle Factors to Improve CVD: Spotlight on Circadian Rhythms and Sleep). These exogenous disrupters, all of which are associated with a modern 24-hour way of life, effectively permit people to ignore the master biological clock cues, often at the expense of the rhythms and bodily processes regulated by the master biological clock. The physiological processes that govern the need to optimize sleep and foster optimal light/dark exposure in one's daily life are reviewed in the following sections.

The Master Biological Clock

The body's circadian rhythms are generated endogenously and continuously aligned with the world around us by exogenous environmental factors, principally the diurnal pattern of light and dark incident on the retinae. Mammalian circadian rhythms are regulated by the suprachiasmatic nuclei (SCN) situated in the brain's anterior hypothalamus. Also known as the master biological clock or simply the "master clock," the SCN free-runs in humans at a natural period that is slightly greater than 24 hours, which over time would lead to asynchrony between our internal behavioral and physiological processes and our external environment.

Based on these inputs, the mammalian master clock synchronizes the body's myriad peripheral clock cells and modulates the physiological processes that are unique to their respective organs and systems (10). In addition to the diurnal light/dark cycles that effectively reset the master clock, other less-robust cues exogenous cues or zeitgebers (literally, "time" + "giver") for promoting synchrony include mealtimes (but not the physical act of eating), social activities, and exercise.

Output Rhythms

"Output rhythms" are behavioral and physiological rhythms regulated by the master clock. Key output rhythms are listed in the following subsections. Of special interest to the present manuscript are the sleep/wake cycle and alertness, core body temperature, and hormone production, especially melatonin and cortisol.

Sleep/Wake Cycle and Alertness

The sleep/wake cycle is one of the most prominent circadian rhythms (12, 13) and is primarily composed of two distinct, independent, and opposing systems (Figure 2): sleep drive (a homeostatic process) and an alerting force (a circadian process) (14) (15, 16). The complementary interaction between these systems ensures that we sleep at night and maintain wakefulness during the day, determining when we fall asleep and how well we sleep. Sleep drive is at its minimum upon waking and steadily gathers in intensity throughout the day, rapidly diminishing within the first hours of sleep. The alerting force is regulated by the master clock and follows a circadian rhythm, reaching its peak during the early evening and its nadir during the second half of the night. Alertness is strongly correlated with the sleep/wake cycle (17).

Sleep Architecture

Sleeping 6–8 hours per day is an important part of a healthy lifestyle, as recently advised in American College of Cardiology/American Heart Association guidance on the primary prevention of CVD (18). Sufficient sleep duration complemented by good sleep architecture is important for health in general, and especially for CV health. Sleep consists of the various stages of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is now divided into three sub-stages: stage N1, stage N2, and N3 based on the new American Academy of Sleep Medicine classification system. These stages are summarized in Table 1. Rapid eye movement sleep has typically been associated with vivid dreaming, based on early studies in which patients were wakened during REM sleep (19). REM sleep accounts for 18–23 % of total sleep time and it is believed to be important for memory consolidation.

Core Body Temperature

Core body temperature (CBT) also follows a circadian pattern (20), maintaining a high level during the day and reaching a peak in the early evening, then lowering at night to reach its nadir about 1.5–2.5 hours before one's natural wake time. The rhythm of CBT is typically in phase with the alerting force and has a negative correlation with the melatonin production rhythm. The alerting force reaches its minimum during the second half of the night, close to attainment of the core body temperature minimum (CBTmin).

Hormone Production

The master clock is known to influence a variety of hormones and endocrine factors (21), but the present discussion is limited to the production of melatonin and cortisol.

Melatonin

Melatonin is produced by the pineal gland. The pineal gland's primary function is to convey light/dark information to the body via the secretion of melatonin (22), a hormone that is easily absorbed into the bloodstream and is therefore an ideal chemical messenger of time-of-day information for the entire body. Melatonin is also involved in the transmission of information concerning day length or photoperiod for the organization of seasonal responses (e.g., breeding) in animals (23). Because melatonin is produced during the subjective night (i.e., the inactive period in diurnal species and the active period in nocturnal species) and in darkness, melatonin levels in diurnal species like humans are low during the day and elevated at night. Researchers hypothesize that melatonin, though not a sleeping pill, can induce sleepiness by acting on the SCN and reducing the "wake-promoting" signal (i.e., the alerting force in Figure 2) issued by the master clock during the day.

Melatonin secretion also has an inverse relationship with core body temperature, which is closely linked to waking and sleep times (Figure 3) (20, 24, 25). Peak melatonin levels typically occur slightly before the core body temperature nadir or core body temperature minimum (CBTmin) that is reached about two-thirds of the way through a sleep episode. In the absence of external cues, endogenous melatonin secretion begins around 9–10 p.m. (or about 2 hours prior to habitual sleep time) and ceases around 7–9 a.m., with the maximum level occurring between 2 and 4 a.m. (26).

Cortisol

Cortisol secretion follows a natural 24-hour cycle. In healthy individuals, the cortisol awakening response occurs about 30 minutes after waking. Levels decline during the day, reaching the lowest levels during the early part of the night. (27, 28). Cortisol plays an important role in regulating and supporting a variety of bodily functions systems, including the cardiovascular, metabolic, homeostatic, cellular, and the central nervous systems.

LIGHT AND CIRCADIAN RHYTHMS

Regulation of Circadian Rhythms by Light

The 24-hour light/dark cycle is the master clock's main synchronizer to the solar day (29). Light can phase advance or phase delay human circadian rhythms, depending upon when it is received by the retinae. For example, light that is applied before the CBTmin, which is reached approximately 1.5–2.5 hours before we naturally wake, will delay the master clock (i.e., one will wake up later the following day), and light applied after the CBTmin is reached will advance the master clock (i.e., one will wake up earlier the following day) (Figure 4) (30, 31). Although light is the main synchronizer of the master clock to the solar day, it is not the only one. Exercise, social activities, timing of the sleep and waking dictated by work and/or family schedules, and scheduled mealtimes also shift and synchronize the clock, but their impact on circadian rhythms appears to be weaker than the impact of light/dark cycles (32).

Lighting Characteristics Affecting Circadian Rhythms

The retinal neural mechanisms involved in processing patterns of light and dark for the functioning of the circadian system are well established. The retina’s rods, cones, and intrinsically photosensitive retinal ganglion cells (33) work together to convert light signals into electrical signals that are conveyed to the master clock in a process called circadian phototransduction (34). The same photoreceptors also supply information to the visual system. As summarized in Table 2, the two systems process their respective classes of information quite differently (35). First, the visual system, for example, is activated at very low light levels, whereas the amount of polychromatic “white” light (like that emitted by architectural lighting or even the sun) required to activate the circadian system is greater by at least two orders of magnitude (36).

Second, the two systems operate quite differently with respect to light’s spectral properties. The performance of the visual system (for tasks like the precise discernment of small/fine details) is most sensitive to middle-wavelength light while the circadian system is maximally sensitive to short-wavelength light. Third, time is also a factor in the differences between the two systems. The visual system’s performance is not significantly dependent on the timing of light exposures and responds well to a light stimulus of short duration at any time of the day or night, whereas the circadian system requires bright days, dim evenings, and dark nights for synchronizing circadian rhythms with the local time on Earth. Disruption of that sequence, especially when it involves exposure to light with the wrong amount and spectral properties (e.g., bright light or short wavelengths) at the wrong time (e.g., prior to the onset of melatonin production in the early evening or in the middle of the night) will almost inevitably lead to circadian rhythms disruption. Fourth, the visual system responds to light stimulus within milliseconds (35), whereas the circadian system’s response can take several minutes and is influenced by prior light exposures experienced over the course of hours, days, weeks, and even months. Greater daytime light exposures (i.e., with respect to light levels and exposure duration) reduce the circadian system’s sensitivity to light generally, as measured by nocturnal melatonin suppression and circadian phase shifting (37). Our work has also illustrated that light’s spatial distribution plays a key role in determining a light stimulus’s circadian effectiveness (38). Specifically, light reaching the nasal retina more effectively stimulates the circadian system compared to other retinal areas, as measured by acute melatonin suppression (38).

THE CLINICAL RISK OF SLEEP AND CIRCADIAN DISTURBANCES

Sleep Disturbances and CVD Risks

Good sleep can be characterized in numerous ways, including sleep quantity (or sleep duration), sleep quality (consolidated versus fragmentary), sleep stages, and the presence/absence of a host of sleep disorders (e.g., insomnia, periodic limb movements and restless leg syndrome, parasomnia, REM sleep behavior irregularities, narcolepsy, sleep apnea, etc.). Activity of the autonomic nervous system, which regulates cardiovascular functions, varies with sleep stages. For example, parasympathetic nervous system tone (39) is highest in stage N3 sleep but sympathetic activation (which increases heart rate and agitation, among other processes) is highest in REM sleep (see below). Sleep is considered restorative when transitions occur without arousals or fragmentations from one sleep stage to another.

Sleep disturbances affect diurnal patterns of blood pressure and heart rate, insulin sensitivity, autonomic nervous system activity, and body mass, and therefore may significantly affect CVD risk. Sleep disturbances may also affect behaviors such as timing of diet and amount of physical activity, which will have an indirect impact on CVD risk (40). For example, sleep deprivation alters the appetite-regulating hormones leptin and ghrelin, leading to increased caloric intake (41). Moreover, it has been shown that sleep deprivation affects brain regions associated with reward behaviors, leading to increased food intake and potential reductions in physical activity levels due to fatigue resulting from short sleep (42). Sleep deprivation may also affect regulation of the hypothalamic–pituitary–adrenal (HPA) axis because cortisol and other glucocorticoids are connected to the sleep–wake cycle. Short sleep can lead to HPA dysregulation, increasing greater alertness that in turn can lead to increased sleep disturbances (43). Sleep regularity is also an important health component. St-Onge and colleagues have shown that increase in bedtime regularity is associated with improvement in body composition and reduction in inflammation, both of which serve to decrease CVD risk (44, 45).

All these factors, alone or in combination, can lead to negative health effects that are associated with increased risk for CVD. For instance, a meta-analysis of 26 articles examining sleep duration's relationship with all-cause mortality and CVD events revealed that short (<7 hours per night) sleep duration was associated with CVD (RR, 1.14 [95% CI, 1.09–1.20]), as was long (>9 hours per night) sleep duration (RR, 1.36 [95% CI, 1.26–1.48]). In addition, studies have identified poor sleep quality as an independent CVD risk factor (46).

Circadian Rhythms Disruption and CVD Risks

Circadian rhythms disruption negatively affects the harmony that should exist between the timing of our pre-programmed master clock and the local, solar light/dark pattern. When that harmony is broken, disturbances in various bodily functions begin to appear, as can happen, for example, after transcontinental air travel. Disruption of the circadian cycle, either by melatonin depletion or by exposure to irregular light/dark cycles, has been shown to affect mortality in some animal models (47).

The vulnerability posed by circadian rhythm disturbances may vary according to the time of day. For instance, in 1985 a landmark paper first reported on how the highest incidence of acute myocardial infarction occurred in the morning hours (between 6 a.m. and 12 p.m.) (48). This morning vulnerability to myocardial infarction and other CVD events has been confirmed by subsequent research (49) and appears to be at least partly due to the circadian system's control of the timing of certain CV functions, establishing that circadian rhythms disruption can profoundly impact CV health (9, 50).

By contrast, nighttime is generally a period of relative protection from CVD events, with myocardial infarction, sudden cardiac death, and stroke occurring less frequently at night compared to the early morning. At night, arterial blood pressure (ABP) and heart rate

(HR) are lower, and cardiac parasympathetic modulation is higher, as modulated by the master clock. However, because ABP and HR decrease during non-REM sleep, and cardiac parasympathetic modulation increases at the beginning of the night, circadian sleep disorders may increase the risk of CVD by desynchronizing these coordinated diurnal heart activities.

Recently Huang et al. (51) reported on the association between the incidence of CVD and circadian rhythms disruption, measured as a high day-to-day variability in sleep duration or timing. According to the authors, deep sleep (or Stage 3 sleep) is known to be associated with a decrease in sympathetic nerve activity, and circadian rhythms disruption leading to sleep disturbances may increase or disrupt sympathetic nerve activity and neurohormonal balance.

Cortisol Circadian Rhythm Disruption and CVD Risks

The circadian rhythm for cortisol directly affects the brain, the autonomic nervous system, the heart, and blood vessels to prepare the cardiovascular system for optimal functioning (52). Disruption of circadian rhythms through increased cortisol levels resulting from prolonged periods of stress have been shown to significantly affect heart health, leading to increased blood cholesterol, triglycerides, blood sugar, blood pressure, and obesity (53). One study proposes a link between a lower cortisol awakening response and higher evening cortisol levels and increased risk for cardiovascular mortality (54). Another study suggests that an increase in total cortisol leads to an increase in inflammation and correlates with the incidence of carotid artery plaques as are found in vascular atherosclerosis (55). Studies have also suggested that an increase in cortisol levels is associated with stroke and linked to poor post-stroke outcomes and mortality (56). In fact, HPA axis dysregulation is present in up to 40% of stroke patients (56).

LIFESTYLE FACTORS TO IMPROVE CVD OUTCOMES: SPOTLIGHT ON CIRCADIAN RHYTHMS AND SLEEP

While electric lighting has brought vast and numerous benefits to humankind, it has also radically transformed the human experience of light and darkness. As we have reviewed, mounting evidence indicates that how we manage our exposures to light and dark can profoundly affect our circadian rhythms and overall health. Many aspects of our modern lifestyle contribute to increased risk for circadian rhythm disturbances, including such factors as working long hours and/or night shifts, 24-hour services and entertainment, the use of self-luminous devices prior to bed, rapid travel across multiple time zones, and irregular sleep schedules (57, 58).

Too little light during the day, combined with exposure to high levels of electric light and self-luminous electronic displays in the evening, can lead to people’s daily schedules shifting later into the night and result in substantial circadian rhythms disruption. Indeed, circadian rhythms disruption by dim, extended, aperiodic light exposure is now probably experienced by most people in modern societies (59).

While we no longer expect everyone to spend their waking hours under the blue sky and to sleep throughout the entire night in total darkness, Figure 5 illustrates the key lifestyle habits that can help one to manage light and dark, reduce circadian disruption, and improve sleep quantity and quality. These habits are discussed below:

Sleep between 7 and 9 hours per night

Chronically short sleep durations (less than 6 hours), and even long sleep durations (greater than 9 hours), have been linked to increased CVD risks. Factors like earlier start times at work or school; expansion of the conventional 8-hour workday into the evening thanks to the ubiquity of email, laptops, texting, and cell phones; an ever-burgeoning obsession with electronic social media when we might otherwise be reading a book or sleeping; long commutes; and our enthusiastic embrace of caffeine have us pushing the boundaries and getting less and less sleep. Ask yourself: do you feel refreshed or energized in the morning? Or do you need to sleep in on weekends to make up for weekday sleep deprivation? If you feel that you need an extra 2 hours or more of sleep on weekends, you might be sleep deprived. Consider adjusting your sleep habits.

Maintain Regular Sleep-Wake Cycles

Sleep regularity is a health optimizer that has been shown to reduce the incidence of CVD. Thus, it is important to maintain consistent and regular bedtimes and sleep durations throughout the entire week, avoiding wide variations between weekdays and weekends. If your sleep duration on weekdays is more than 2 hours shorter than on weekends, for example, you may be suffering from circadian misalignment or social jet lag (58). If your work and social schedules present a fixed wake time, it is best to maintain an earlier bedtime to ensure adequate sleep.

Get as Much Morning Daylight as You Can

The best light for circadian entrainment is daylight. If you can, spend 1 or 2 hours outdoors, the earlier the better. Go for a walk, sit on your deck, or go for a car ride. Even with closed car windows you will receive sufficient light at the eyes. Open the window shades in your home or office but be careful to avoid creating glare. If you are going out for lunch, try to sit outside; if you must remain indoors, try to sit next to a window or other source of daylight. When sitting by a window, try to face it rather than sit with your back toward it. Light has to reach your eyes to be effective for the circadian system. Unless you live with light sensitivity, or if your morning commute involves driving into direct sunlight and would compromise your safety on the road, try going without your sunglasses. The greater the amount of light you get after daybreak, the better. Make sure you are exposed to light at the same time every day, preferably early in the day.

Increase Light Exposures Throughout the Entire Day

Light levels in today’s built environment, especially for those working from home or in windowless offices, are lower than those needed to affect the circadian system. If you cannot work facing a window, add extra table or floor lamps next to your work area (Figure 6). A do-it-yourself (DIY) circadian lighting device is another option (60). If you have access to windows, make sure the shades are open and that you are facing the window.

If you are embarking on new construction or retrofitting existing windows, it would be worthwhile to explore some of the emerging "smart window" technologies. Recent field work by our research team, for example, studied the effects of circadian-effective light exposures facilitated by electrochromic glass windows among 20 apartment-dwelling residents in Reston, Virginia (61). This 4-week, crossover, within-subjects study employed objective measures of sleep and circadian alignment (i.e., actigraphy and dim light melatonin onset) and subjective measures (i.e., surveys) of sleep, health, mood, lifestyle factors, and feelings of vitality. The results showed that compared to participants living in apartments fitted with conventional glass windows and blinds, those in apartments fitted with electrochromic glass windows demonstrated greater circadian alignment, earlier and more regular sleep, and improved vitality and mental health.

Reduce Evening Light Exposures

Your melatonin levels typically start rising about 2 hours prior to your normal bedtime. Reduce evening light exposures at this time by dimming the lights at home. Turn off your self-luminous displays 2 hours prior to bedtime. If you cannot turn them off, at least dim the brightness level and/or reverse the display's color scheme to show a black background with white text.

Conclusions

The advent of electric lighting in the built environment has radically transformed the human experience of light and darkness. Electric light in the built environment can be insufficient to stimulate and synchronize the master clock to the day-night cycle, leaving us in "circadian darkness," (35), meaning that our lighted environment does not produce sufficient stimulus for the master clock and hence the circadian system. Humans require a robust, regular daily schedule of exposures to light and dark for maintaining circadian entrainment. The lack of entrainment of the circadian system (or circadian misalignment) leading to poor sleep could be an important biophysical mechanism underlying the increased incidence of certain types of diseases, including CVD, in industrialized societies. Specific lifestyles behaviors, such as seeking bright light during the day and reducing evening light exposures can promote circadian entrainment, improve sleep quality, and increase the overall brightness of your day.

Acknowledgements

The research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK128972) and the National Institute for Occupational Safety and Health (R01OH010668).

ALPHABETICAL ABBREVIATIONS

ABP	arterial blood pressure
CBT	core body temperature
CV	cardiovascular
CVD	cardiovascular disease
HPA	hypothalamic–pituitary–adrenal

HR	heart rate
NREM	non-rapid eye movement
REM	rapid eye movement
SCN	suprachiasmatic nuclei

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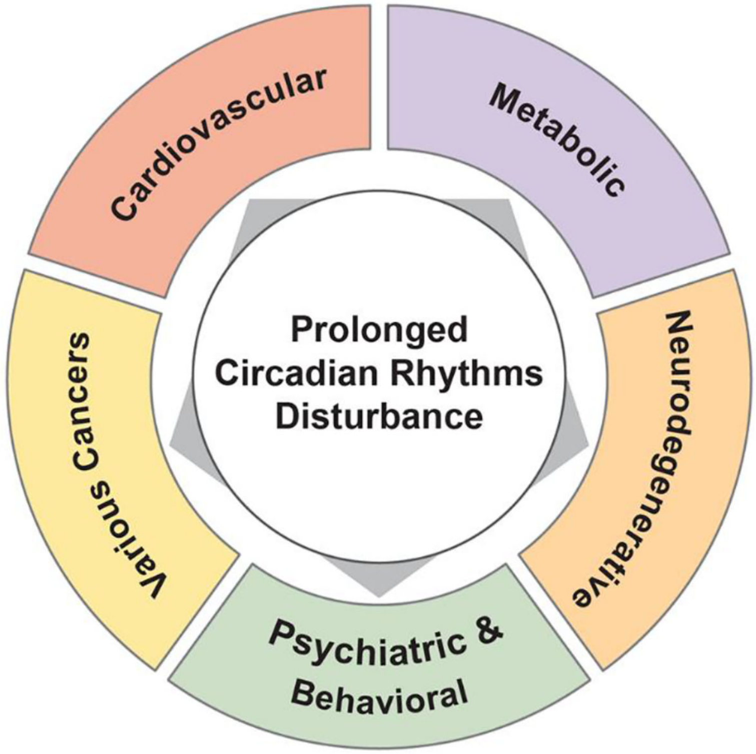

Figure 1.
Diseases linked to circadian rhythm disturbances.

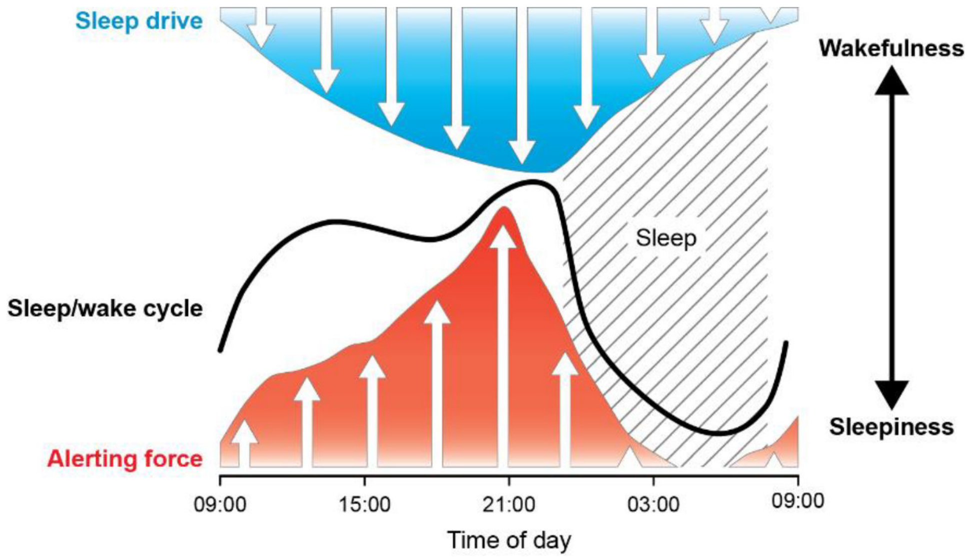

Figure 2.
Schematic of the sleep/wake cycle governed by two opposing systems: sleep drive (homeostatic) and the alerting force (circadian). Adapted from Dijk and Edgar (14).

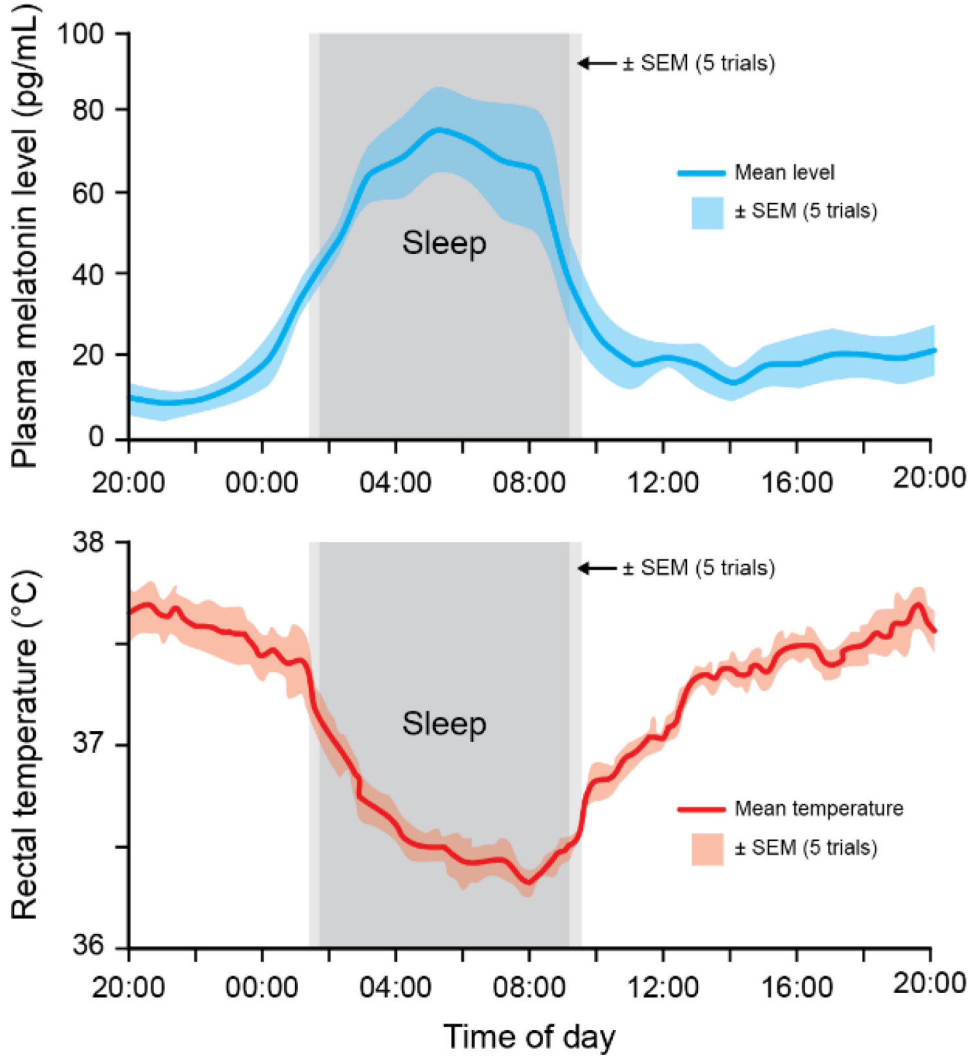

Figure 3.

The inverse relationship between circadian rhythms in plasma melatonin (top) and rectal temperature (bottom) in single experimental subject, showing mean values and ± SEM obtained over five trials. Adapted from Hashimoto et al. (25).

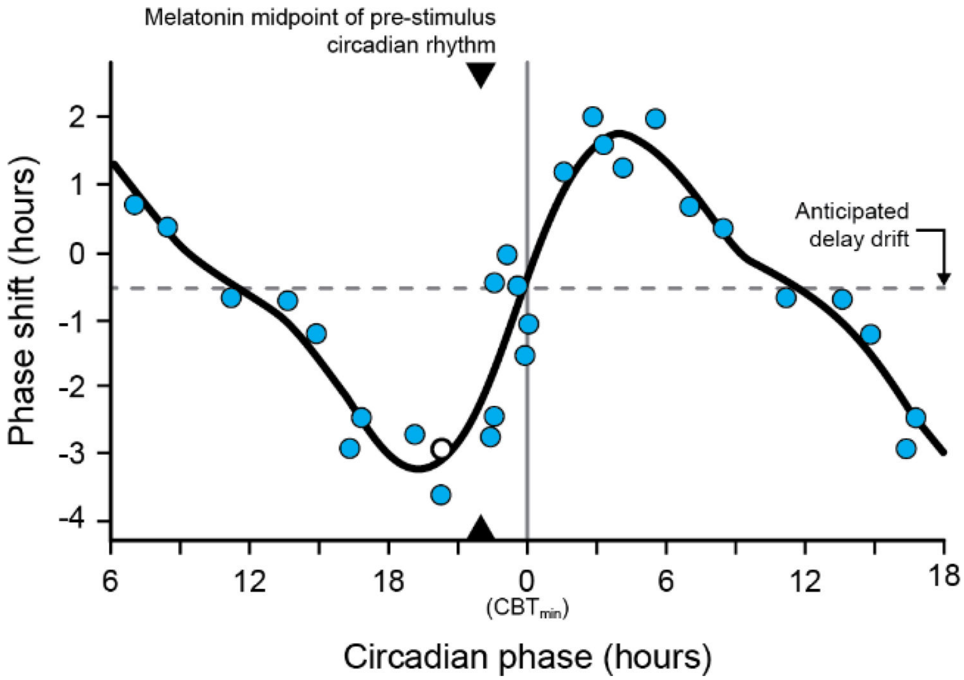

Figure 4.

Phase response curve (solid black line) calculated by Khalsa and colleagues for phase delay in response to a 6.7-hour bright light exposure, relative to circadian rhythms recorded prior to the exposure. The curve is plotted relative to the pre-stimulus melatonin midpoint's phase (22 hours), represented by the solid triangles, before the CBTmin 2 hours later (0 hours). The horizontal dashed line represents the pacemaker's anticipated mean delay drift (0.54 hour) between the study's pre- and post-stimulus assessments. The solid blue data points were obtained from plasma melatonin and the open data point was obtained from salivary melatonin. A negative number represents the estimated phase delay resulting from the light exposure and a positive number represents the estimated phase advance resulting from the light exposure. Adapted from Khalsa et al. (30).

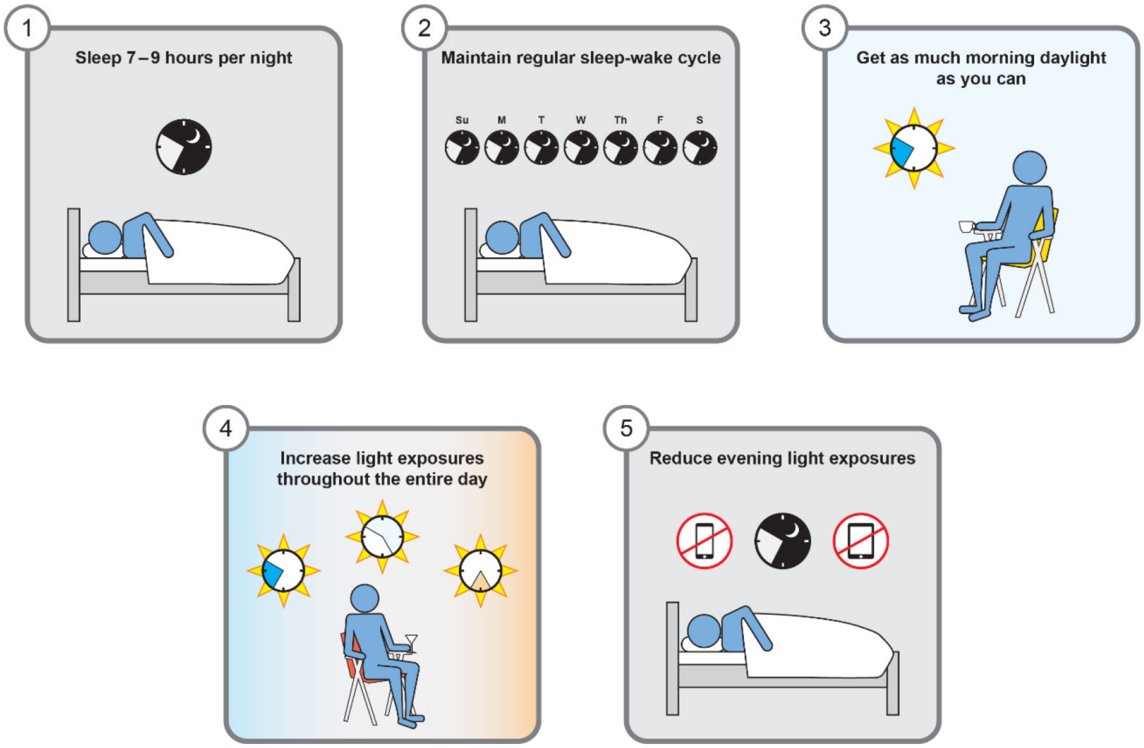

Figure 5.
Lifestyle factors to improve CVD outcomes.

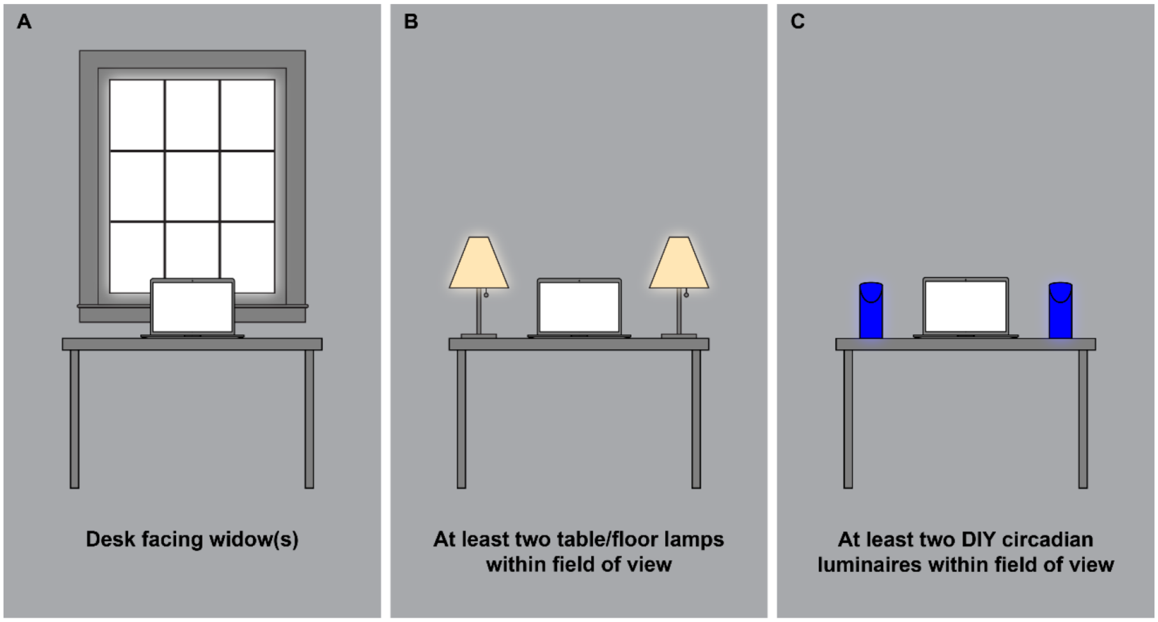

Figure 6.
Light levels in the built environment are often too low for stimulating the circadian system, especially for those working from home or in windowless offices. This can be remedied by facing a window while working (A) or adding extra lamps next to your work area (B) or even a do-it-yourself (DIY) circadian lighting device (C).

Table 1.

Stages of NREM sleep

Stage	Description
N1	• Stage N1 sleep is how humans typically transition from wakefulness to sleep • Lightest stage of sleep • Typically accounts for 5–10 % or less of the total sleep time in young adults
N2	• Stage N2 sleep generally represents the largest percentage of total sleep time in a normal middle-aged adult • Typically comprises 45–55 % of a sleep epoch
N3	• Stage N3 sleep, frequently referred to as “deep sleep” or “slow-wave sleep,” is the deepest NREM sleep stage • Accounts for 10–20 % of the total sleep time in young to middle-aged adults • Sleep time in N3 decreases with age • Occurs mostly in the first half of the night since slow-wave activity during sleep represents the homeostatic drive to sleep, which is the greatest after the all-day waking period

Table 2.

Salient characteristics of the responses of the visual and circadian systems to salient lighting characteristics

LIGHTING CHARACTERISTIC	VISUAL SYSTEM RESPONSE	CIRCADIAN SYSTEM RESPONSE
Light levels	The visual system is activated by very low light levels	The circadian system is activated by higher levels of light
Spectral sensitivity	Most sensitive to middle- wavelength light (peak spectral sensitivity ~ 550 nanometers	Maximally sensitive to short- wavelength light (peak spectral sensitivity ~ 460 nanometers)
Timing of exposures	Not significantly dependent on the timing of light exposure and responds well to light stimulus of short duration day or night	Requires bright days, dim evenings, and dark nights for synchronizing circadian rhythms with local time
Response time	Responds to light stimulus within milliseconds	Response can take several minutes and is influenced by prior light exposures, from a few hours to several months
Light exposure history	Not significantly affected by history of light exposure	Affected by both short- and long- term history of light exposure