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Sleep and circadian rhythms: pillars of health—a Keystone Symposia report

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The human circadian system consists of the master clock in the suprachiasmatic nuclei of the hypothalamus as well as in peripheral molecular clocks located in organs throughout the body. This system plays a major role in the temporal organization of biological and physiological processes, such as body temperature, blood pressure, hormone secretion, gene expression, and immune functions, which all manifest consistent diurnal patterns. Many facets of modern life, such as work schedules, travel, and social activities, can lead to sleep/wake and eating schedules that are misaligned relative to the biological clock. This misalignment can disrupt and impair physiological and psychological parameters that may ultimately put people at higher risk for chronic diseases like cancer, cardiovascular disease, and other metabolic disorders. Understanding the mechanisms that regulate sleep circadian rhythms may ultimately lead to insights on behavioral interventions that can lower the risk of these diseases. On February 25, 2021, experts in sleep, circadian rhythms, and chronobiology met virtually for the Keystone eSymposium "Sleep & Circadian Rhythms: Pillars of Health" to discuss the latest research for understanding the bidirectional relationships between sleep, circadian rhythms, and health and disease.

Keywords: appetite control; biomarkers; circadian misalignment; circadian rhythm; food timing; shift work; sleep; sleep duration; sleep homeostasis; social jetlag

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Introduction

Circadian rhythms are driven by a circadian clock generating an endogenous near 24-h oscillation in the human brain: sleep/wake cycles, body temperature, blood pressure, drug metabolism, hormone secretion, kidney function, gene expression, drinking rhythms, and immune system functions all display a diurnal rhythm. The most important synchronizing cue (zeitgeber) affecting the circadian clock is light.[1] In particular, short-wavelength blue light triggers the melanopsin retinal receptors in the eye and entrains the central clock in the suprachiasmatic nuclei (SCN) in the hypothalamus. Light stimulates the activity of SCN neurons, sending synchronizing signals throughout the body. Some evidence suggests that the timing of certain nonphotic stimuli—such as sleep, physical activity, and food intake—may also impact the central clock.[2] A key marker of the circadian system is melatonin, the production of which is suppressed by light and, therefore, occurs almost exclusively at night.[3] Changes in peripheral melatonin levels provide clues into the status of the circadian system in animal and human studies.

The central clock in the brain acts as a master pacemaker for other molecular clock in peripheral organs. Similar to the SCN clock, these clocks consist of transcriptional activators and repressors, such as CLOCK-BMAL1 and PER-CRY, that coordinate metabolic functions with sleep/wake and feeding–fasting cycles.[4] Desynchronization of the central and peripheral clocks can impact hormones and cell functions that can affect disease risk.

For many people, work schedules, travel, and social activities mean that sleep and meal times often do not align with biological signals. This can impair circadian rhythms in physiological parameters, including blood pressure, glucose levels, hormones, and vigilance, thereby contributing to increased chronic disease burden, and increasing the risk of cancer, cardiovascular disease (CVD), and cognitive impairment/accelerated aging.

On February 25, 2021, experts in circadian biology and sleep met virtually for the Keystone Symposium "Sleep & Circadian Rhythms: Pillars of Health" (Box 1). A major goal of the meeting was to develop a multidisciplinary approach to the understanding of the bidirectional relationship between lifestyle behaviors, health outcomes, and sleep and circadian rhythms in humans. The meeting covered the interactions between lifestyle and circadian rhythms, exploring biological mechanisms, functional and clinical significance, and ultimately their impact on health.

The first half of the meeting focused on the relationship between circadian rhythm disruptions and chronic disease risk. Presenters discussed recent data on the timing of sleep and food intake on chronic disease risk and elucidated some of the genetic, biologic, and molecular mechanisms underlining the links between lifestyle behaviors and health. During the second half of the meeting, presenters focused on disturbances of sleep and circadian rhythms and the resulting impacts on health. Presenters also delved into preliminary evidence of restoring circadian rhythms by improving sleep behavior to ameliorate health outcomes.

Circadian rhythms and chronic disease risk

The first half of the conference focused on the association between circadian disruption and chronic disease risk. Speakers presented epidemiologic evidence on the negative effect of circadian disruption on cancer and CVD risk in rotating night shift workers. They also presented data on the genetic and molecular mechanisms that regulate appetite and meal timing and provided evidence for the impact of meal timing on CVD and metabolic disorders.

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Impact of circadian disruption on chronic disease risk in night shift workers

Circadian misalignment and ultimately circadian disruption is associated with an increased risk of chronic diseases, including cancer, CVD, and metabolic diseases. One contribution to circadian misalignment in the modern era is increased light at night.[5] To investigate the impact of light at night and disrupted circadian patterns on disease, many studies have examined the risk of chronic diseases among night shift workers. Night shift work encompasses a number of circadian disruptions that are tightly linked to the changed light exposure during night work, including disruptions in sleeping, eating, and activity. Night shift workers provide a particularly useful model to understand the impact of wakefulness and light at night for several reasons: (1) they are often chronically exposed to light at night, often several days a month for years; (2) they are subjected to high levels of ambient light, particularly at night; and (3) they usually cannot change their exposure, as opposed to people who choose to stay up late in their free time.

Two speakers presented data on the risk of shift work on chronic disease from the Nurses' Health Studies (NHS).The NHS consists of three ongoing cohort studies, dating from 1976. Over 300,000 female nurses have been enrolled, approximately 60% of whom have worked night shifts. Participants provide medical, lifestyle, and behavioral information, as well as blood and urine samples, and are regularly followed up for longitudinal data.

Eva Schernhammer from Harvard Medical School and the Medical University of Vienna discussed her work using the NHS to understand the impact of shift work on cancer risk. A mechanistic link between light at night and breast cancer was proposed over 30 years ago. The melatonin hypothesis purports that increased light at night decreases melatonin levels, which increases estrogen levels and leads to a higher risk of breast cancer.[6] The melatonin hypothesis is supported by population-based studies. In the NHS, shift work increased the risk of breast cancer by up to 80%, with risks increasing as the length of time on night shifts increased.[7,8] Higher melatonin secretion was associated with a lower breast cancer risk.[9,10] An updated analysis of the NHS, with over 24 years of follow-up and 6000 breast cancer cases, confirmed the association between night work and breast cancer risk. The study also demonstrated that breast cancer risk resembles that of non-night working women when shift work ceases.[11] Another study correlated high light at night near participants' homes with a significantly elevated risk for breast cancer. The increased risk was restricted to premenopausal women and mostly associated with estrogen receptor positive tumors.[12]

While the most robust data are for breast cancer, Schernhammer has also shown that shift work increases the risk of colorectal cancer (CRC), endometrial cancer, and lung cancer in the NHS.[13–16] In addition, over 20 studies have examined the association between night work and various cancers in men, including prostate, gastrointestinal, and lung cancer, with most demonstrating a dose–response relationship between duration of night work and cancer risk.[15–19]

In 2007, the International Agency for Research on Cancer (IARC) classified shift work as a Class 2A carcinogen based on the epidemiologic data. This has prompted some countries to compensate night shift workers who develop breast cancer.[17] In 2019, the IARC re-evaluated the carcinogenicity of night work due to the large number of new epidemiologic studies that had been published since their initial report.[18] The new report reaffirms the classification of night work as a Group 2A carcinogen on the basis of limited evidence that night shift work causes breast, prostate, and CRC, with insufficient evidence for other cancer sites. Current epidemiological data are supported by sufficient evidence in animal models and strong mechanistic evidence in experimental systems. The agency called for more research in humans on the mechanisms underlying this increased risk, such as the impact of night work on oxidative stress, immunosuppression, inflammation, genotoxicity, and epigenetics. Schernhammer stressed that human studies on the effect of shift work on cell proliferation, cell death, and nutrient supply are lacking. She called upon researchers to fill these gaps. Schernhammer ended her presentation with a quote from leading chronobiologist Erhard Haus, who stressed that cancer is just one aspect of the shift work problem.

As **Céline Vetter** from the University of Colorado, Boulder showed, there is strong evidence for an adverse but modest effect of shift work on

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heart health as well.[19] There is a large amount of heterogeneity between studies, however. To generate more robust data, Vetter conducted a large analysis of over 150,000 participants with 24 years of follow-up data in the NHS2. People who had performed 5 years of rotating shift work had a 12% increase risk of myocardial infarction. Similar to the findings of cancer studies, longer duration of shift work was associated with a higher risk, with reduction in risk if an individual stopped doing shift work.[20] Vetter is also examining other large datasets, such as the UK Biobank, to see if these results can be replicated in other populations. Shift work imposes disruption on several aspects of the circadian rhythm. Typically, the disruption of shift work is modeled by shifting the sleep cycle with respect to melatonin rhythm.

Vetter described other ways to model the disruption, such as repeated phase shifts in the melatonin rhythm as the body continually attempts to resynchronize with the light–dark cycle and a loss of rhythmicity and/or dampening of the amplitudes of the melatonin cycle.[5]

Vetter also described some of the mechanistic evidence for circadian misalignment and increased risk of heart disease. In laboratory settings, sleep deprivation has been associated with an increase in biomarkers of CVD risk and blood pressure.[21–24] Results in shift-work settings are mixed, likely due to differences in shift-work schedules and study designs.[25–29] However, in field settings, circadian misalignment and sleep deprivation co-occur and show significant and clinically meaningful interindividual differences by chronotype.[30–34] Vetter proposed that increased heterogeneity in the association between shift work and CVD risk in real-world settings is partially due to higher heterogeneity in chronotype that, together with mixed schedules, creates more variable exposure.[31,34,35] While it can be difficult to assess circadian phase in shift workers, there are several behavioral proxies of circadian misalignment[36–39] that Vetter hopes can be leveraged in large cohort studies.

Vetter ended by describing efforts to improve heart health by prioritizing alignment of circadian rhythms. Studies have shown that improving sleep hygiene can reduce inflammation, oxidative stress, and insulin resistance, and ameliorate metabolism.[40,41] It stands to reason that these effects could cumulatively reduce the risk for heart disease.

Vetter's work has shown that schedule adjustments among shift workers to remove the most burdensome shifts based on an individual's chronotype improved sleep quality.[42] Since irregular sleep has been associated with higher CVD risk and longer sleep times have been shown to reduced CVD risk, Vetter hopes that interventions like these will ultimately translate to better heart health in this vulnerable population.[43]

Impacts of meal timing on circadian misalignment and cardiovascular risk

In addition to light, food is a key stimulus for circadian rhythms. Eating patterns in the United States have become more erratic over the past several decades,[44] with a tendency toward later eating times. U.S. adults tend to eat around the clock, with significant day-to-day and weekday-to-weekend variability.[36] Eating at unconventional circadian times, such as consuming more calories in the evening or irregular, variable eating patterns, can misalign the organ and brain clocks, resulting in cardiometabolic dysfunction and increasing the risk of cardiometabolic disease.

Evidence on the role of meal timing in cardiometabolic health is limited. Observational studies suggest an association between later eating and increased cardiometabolic risk.[45–49] In addition, those with more regular eating schedules tend to have lower rates of metabolic syndrome,[50–52] while eating jetlag, that is, large variability in weekday and weekend eating times, was associated with increased body mass index (BMI).[53] Most of these data are from European populations; there are few studies on eating pattern variability and cardiometabolic risk in the United States. A 2017 statement by the American Heart Association (AHA) called for more population studies to clarify the influence of meal timing, particularly related to the evening meal, on cardiometabolic outcomes.[54]

Nour Makarem from Columbia University Irving Medical Center has been working to address this gap. She presented data from two studies evaluating the associations of eating pattern timing and regularity with cardiometabolic risk factors. Makarem presented unpublished data on one of the first population-based studies on meal timing and cardiometabolic health in the United States. The study includes over 12,000 participants in

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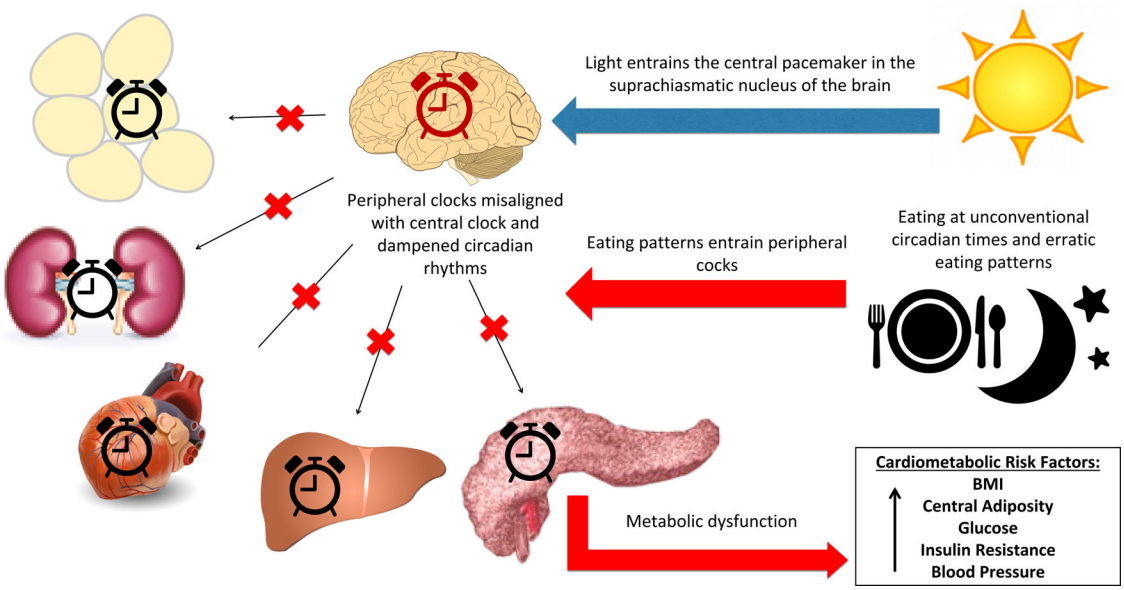

Figure 1. Later eating timing and variable eating patterns may increase cardiometabolic risk via circadian disruption.

the Hispanic Community Health Study/Study of Latinos to investigate whether nighttime eating is associated with diverse metabolic outcomes, such as fasting glucose levels, insulin resistance, and blood pressure.[a]

In another study, Makarem investigated whether variability in daily eating patterns and eating jetlag are associated with cardiometabolic risk in a community cohort of 115 women in the AHA Go Red for Women Strategically Focused Research Network (forthcoming in *JAHA*, 2021). Over the 1-year follow-up, greater day-to-day variability and eating jetlag in nighttime eating, and span of eating period were associated with higher blood pressure and adiposity. Greater day-to-day variability in nighttime eating and timing of the first and last eating session was associated with poor glycemic control. Makarem concluded that an eating pattern characterized by variability in eating timing, duration, and nighttime eating may contribute to cardiometabolic disease (Fig. 1).[55]

Makarem's results suggest that eating schedules characterized by earlier and regular eating timing and duration and less nighttime eating may lower CVD risk, particularly in women. She stressed that longer-term studies in diverse cohorts are needed to confirm these results.

Regulating eating and appetite: molecular, neurologic, and genetic mechanisms

Several speakers presented data on the mechanisms underlying appetite, eating, and connections to metabolic health.

Jonathan Cedernaes from Northwestern University and Uppsala University discussed his work on understanding the neurological mechanisms that regulate appetite.

In mice, knocking out *Clock*, a key component of the molecular circadian clock in pacemaker neurons of the SCN, results in an obese phenotype characterized by metabolic syndrome and mistimed feeding.[56] Cedernaes is interested in understanding how the central clock network in the hypothalamus contributes to disrupted appetite and eating. This network comprises energy-sensing neurons that can regulate functions like insulin sensitivity, insulin output, and glucose production in the liver.[57]

To study the role of the central clock in appetite, Cedernaes *et al.* characterized the effects of hypothalamic knockout of the core clock gene *Bmal1* in mice.[58] Similar to *Clock* knockout mice,[56]

[a]https://www.ahajournals.org/doi/abs/10.1161/circ.138.suppl_1.11503

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Bmal1 knockout mice had an eating schedule skewed toward the day, the resting period for those animals. They also had an obese phenotype, despite consuming a similar amount of calories as the wild-type mice. Cedernaes showed that mistimed feeding can lead to dysregulated metabolism. Mutant mice show increased glucose production by the liver, which was not suppressed by glucose infusion, as well as signs of reduced insulin sensitivity. Time-restricted feeding, that is, feeding mice during the night normalized glucose output as did severing the vagal nerve connecting the brain and liver.[58]

Cedernaes next looked at the circadian transcriptional activity in agouti-related protein (AgRP) neurons, which are known to regulate appetite. Knocking out *Bmal1* in AgRP neurons increased glucose output, altered the feeding rhythm, and increased body weight. Knockout of *Bmal1* changed the diurnal transcriptional activity in AgRP neurons, resulting in the upregulation of inflammatory pathways and downregulation of several metabolic pathways involved in *Clock* function. He showed that leptin signaling, which is normally increased in the morning during times of fasting, had a more pronounced effect on transcription in *Bmal1* knockout AgRP neurons than in wild-type neurons. Cedernaes concluded that the clock gene *Bmal1* is essential for the morning/evening response to leptin in AgRP neurons. Ablation of the endogenous clock in AgRP neurons shifts the timing of the transcriptional response to leptin and ultimately leads to mistimed eating and metabolic dysregulation.

Erin C. Hanlon from the University of Chicago described work on understanding how the endocannabinoid (eCB) system contributes to food intake. The eCB system is likely best known as the target of Δ^9 tetrahydrocannabinol, an active component of marijuana. The eCB system consists of two G protein–coupled receptors found in both the brain and in peripheral organs involved in energy metabolism. Cannabinoid-1 receptor (CB1) is known to increase appetite and hedonic feeding and has been a drug target for modulating food intake to reduce weight. CB1 inhibitors have been shown to induce weight loss, reduce fat mass, and improve metabolic disorders; however, they were also associated with mood disturbances. The role of cannabinoid-2 receptor (CB2) in appetite is less well understood. CB1 and CB2 are activated by the endogenous ligands 2-arachidonoylglycerol (2-AG) and anandamide (AEA).

Hanlon focused on the role of the endocannabinoid system in feeding and reward, that is, hedonic feeding, during periods of sleep deficiency. Sleep deficiency is known to increase hunger and appetite, particularly for snacks and foods high in hedonic value. She showed that serum levels of the endocannabinoid 2-AG show a robust circadian rhythm in healthy, lean volunteers, with a minimum during the mid-sleep period and a peak in the afternoon. The rhythm is distinct from that of other cyclical hormones involved in metabolism, such as cortisol and leptin, which peak in early morning and middle of night, respectively. In subjects with restricted sleep (i.e., 4.5 versus 8.5 h), the circadian rhythm of 2-AG showed a similar shape, but the peak was shifted approximately 2 h later and had a higher amplitude.[59] The delay in 2-AG peak may affect appetite in the afternoon and evening, while the higher peak may contribute to the risk of overeating. Sleep-restricted individuals reported higher rates of hunger and desire to eat and tended to eat more snacks in the afternoon, at about the time that 2-AG levels were highest, compared with individuals with normal sleep.[59]

Obesity also affected the circadian rhythm of 2-AG. In individuals with obesity, the 2-AG rhythm was delayed and the amplitude flattened compared with normal weight individuals. There was also an association between higher BMI and later 2-AG minimum. This study did not assess whether individuals with obesity ate later than those with normal weight. However, they are consistent with findings that later eating is associated with obesity. It remains to be seen whether the misaligned 2-AG rhythm is a cause or an effect of later eating.[60]

Hanlon showed that the other endocannabinoid, AEA, also displays a circadian rhythm distinct from that of 2-AG in young, lean volunteers. Unlike 2-AG, the AEA rhythm was not affected by sleep restriction.[61] These data suggest that AEA and 2-AG have different roles in physiology, specifically with regard to regulating food intake. Hanlon proposed that AEA may be involved in initiating calorie intake, while 2-AG maintains calorie intake.

While both Cedernaes' and Hanlon's work show a connection between eating timing and metabolic dysfunction, questions remain regarding the factors that affect eating times.

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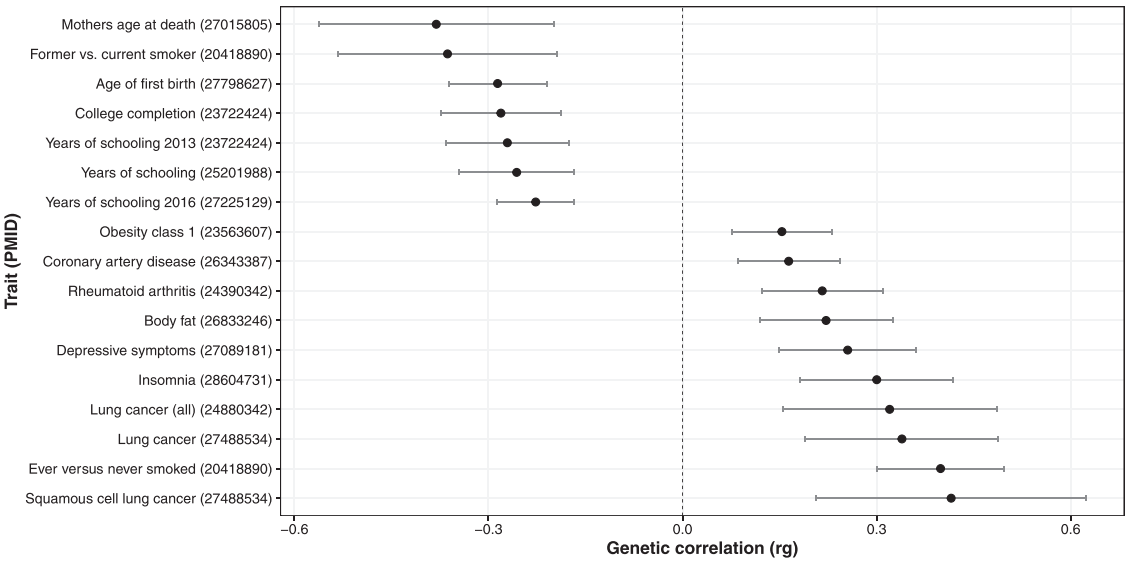

Figure 2. **Cross-trait genetic correlations between breakfast skipping and publicly available traits and diseases using LD-score regression. Only significant correlations with $P < 0.00022$ accounting for 227 tested traits are shown. Point estimates are rg correlations. Error bars indicate 95% CI of rg estimates. PMID, pubmed ID; rg, correlation estimate.**

Hassan S. Dashti, from Massachusetts General Hospital, showed that genetic factors also play a role in when people do and can eat, in addition to many behavioral and societal factors. Delineating the genetic factors behind complex human behaviors like food timing can help to identify biological pathways related to food timing, pinpoint molecular targets for drug development, develop tools to predict vulnerable populations, develop personalized treatment approaches, and elucidate correlations and causal effects with other traits and diseases.

Several lines of evidence suggest that food timing may be partially heritable. Food timing–related eating disorders, such as night eating syndrome and sleep-related eating disorder, show strong family-based heritability.[62] In the general population, findings from a classical twin study show that food–timing heritability ranges from 30% to 60%, with breakfast and lunch timing showing greater heritability than dinner timing.[63]

To identify genetic factors associated with food timing, Dashti conducted a genome-wide association study (GWAS) of 190,000 adults in the UK Biobank.[64] Food–timing information is typically not collected in large cohorts, so Dashti used a proxy phenotype approach, using information on breakfast cereal consumption as a proxy for breakfast skipping. Proxy phenotypes are not uncommon in GWAS studies; for example, education level is often used as a proxy of intelligence.[65] Six independent genetic variants were associated with breakfast skipping. These variants were in regions also known to be associated with schizophrenia, caffeine metabolism, carbohydrate metabolism, and a preference for sweet foods. Three genes were known to be involved in regulating the pace of the circadian clock. Breakfast-skipping genes were enriched in the cerebellum, which is implicated in sleep duration, and are shared with other cardiometabolic traits and diseases. Genetics of breakfast skipping were correlated to that of obesity, body fat, lung cancer, rheumatoid arthritis, depressive symptoms, insomnia, and smoking (Fig. 2). The results suggest that there exists a common set of genes that underlie both food timing and obesity.[66]

A separate study further examined the connection between obesity genetics and food timing in the ChooseWell 365 cohort at Massachusetts General Hospital.[67] The cohort consisted of 397 hospital employees, with data on cafeteria purchases, self-reported eating habits, and genome-wide genetic data. Unlike the GWAS, the ChooseWell 365 analysis included objective data on food purchases to estimate food timing. Using 3 months of food transactions, Dashti showed that employees with higher

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polygenic obesity risk scores tended to purchase their breakfast meals later. Higher polygenic obesity scores were also associated with more food purchases and lower quality purchases.[68]

Dashti's work shows that food timing is at least partially heritable. Genes related to food timing are also involved in circadian rhythms and obesity, supporting the connection between meal timing and cardiometabolic health.

Sleep and circadian disturbance

The second half of the symposium focused on how disturbances to sleep and circadian rhythms can affect health.

Addressing light at night to improve sleep hygiene

Many people are exposed to short-wavelength (blue) light during the day and in the hours before sleep. There is increasing use of light-emitting diodes (LED), which are enriched in short-wavelength light, both inside and outside the home. Outside, LED light sources are replacing older street lamps.[69] Inside, people are exposed to short-wavelength light via computers, smartphones, tablets, televisions, and, increasingly, domestic light bulbs. The Sleep in America poll in 2011 found that over 90% of American adults reported using some type of light-emitting electronic device within the hour before bedtime.[70] While LED lights are more energy efficient and cost-effective than older light sources, they are also likely impacting human sleep and health. This is because the human circadian photoreceptor system, via intrinsically photosensitive retinal ganglion cells, shows peak sensitivity to ∼450–480 nm light within the short-wavelength portion of the visible spectrum.[71]

Ari Shechter from Columbia University presented work on understanding whether reducing exposure to short-wavelength light during the evening preceding bedtime could improve sleep. In laboratory settings, exposure to short-wavelength/blue light in the evening from LED-backlit computers and self-luminous personal devices, such as tablets, was associated with factors that could contribute to impaired sleep initiation and worsened sleep quality, including decreased and delayed melatonin secretion, and increased neurocognitive arousal, core body temperature, and heart rate.[72–78]

As the deleterious effects of short-wavelength/blue light on sleep have become more widely known, the use of blue-light filters on electronic devices in the evening has been embraced by some people. Devices have also begun automatically changing their wavelength distribution after a set time. However, a recent study showed that even when blue-light filters are used, the blue light emitted can still be above the threshold expected to adversely impact the circadian system.[79]

Shechter is interested in determining whether wearable lenses that block or reduce the transmission of short-wavelength/blue light to the retina, and that ultimately affect the circadian and sleep-regulating regions of the hypothalamus, can mitigate some of the adverse impacts of exposure to this light on sleep. Studies have shown that blue-blocking lenses protect against light-induced melatonin suppression and improve self-reported and objective sleep measures. For example, blue-blocking lenses have been shown to maintain melatonin secretion in people exposed to nighttime LED light[80] and to improve sleep in individuals with sleep difficulties.[81] Shechter's work has shown that using blue-blocking lenses in the evening can improve insomnia symptoms and increase objective sleep duration in individuals with insomnia.[82]

To understand the current state of the evidence for blue-blocking lenses on sleep, Shechter and colleagues conducted a systematic review and meta-analysis on studies using the blue-blocking lenses approach during the evening hours to determine their effect on nocturnal sleep. Among the studies that included objective estimates of sleep, there were small-to-medium combined effect sizes for improvements in sleep efficiency and total sleep time (Fig. 3). Comparatively larger effects were seen for subjective measures of sleep, with medium-to-large combined effect sizes observed for Pittsburgh Sleep Quality Index ratings and self-reported total sleep time.[83] Overall, there is some modest evidence that this approach can be beneficial for nocturnal sleep, particularly in individuals with sleep disturbances (e.g., insomnia symptoms and delayed sleep phase syndrome) or psychiatric conditions (e.g., bipolar disorder and attention-deficit hyperactive disorder).

Shechter noted that there was significant heterogeneity in the literature with regard to study designs,

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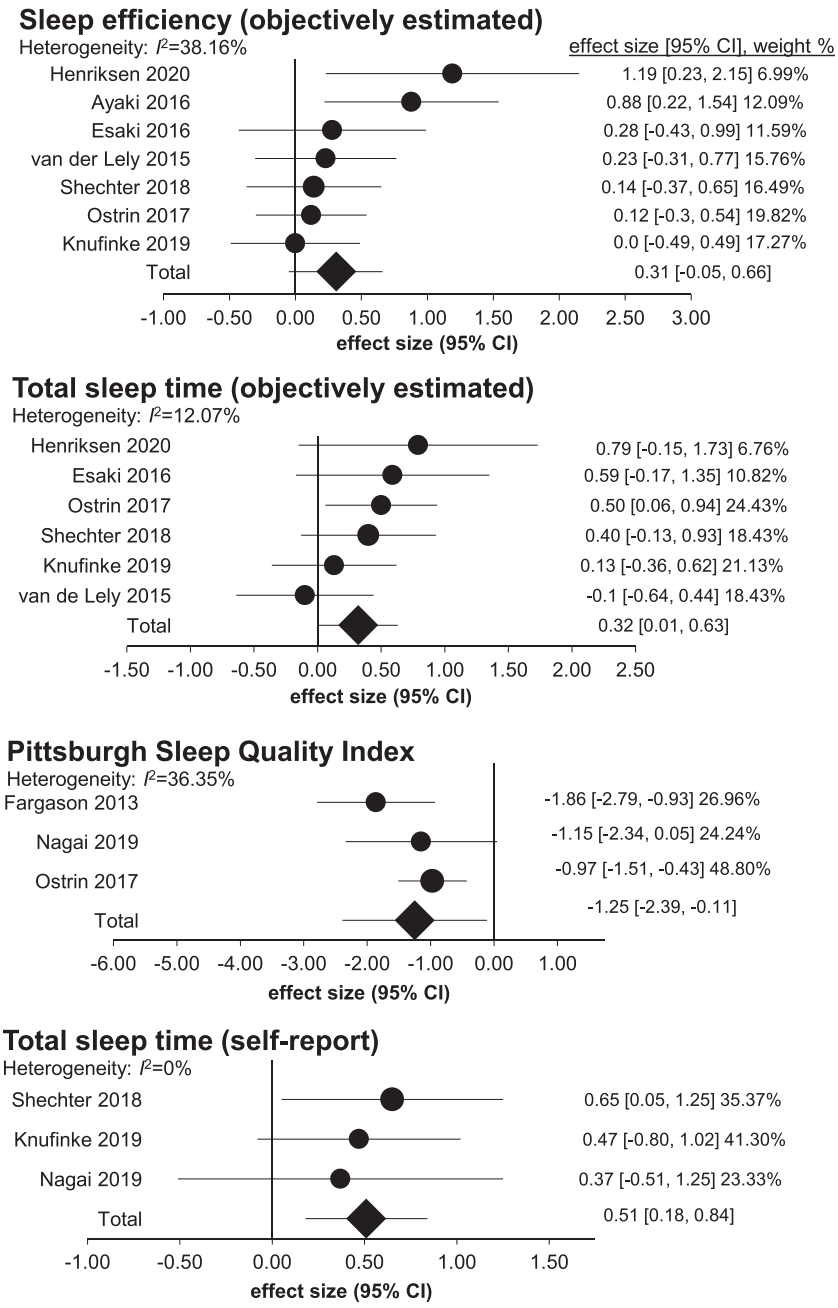

Figure 3. **Forest plots of combined effect sizes from the meta-analyses of "blue blocker" interventions at night and their effects on sleep. Shown are the findings from objectively estimated measures of sleep efficiency and total sleep time, and self-report measures of sleep quality (Pittsburgh Sleep Quality Index rating) and total sleep time. From Ref. 83.**

populations tested, duration of intervention, and the spectral and light intensity transmission of the lenses. Future studies should include standardized sleep-related outcomes, assessments of melatonin and other circadian markers to determine the intervention's potential biological mechanisms of action, and assessments of ambient light levels and spectral composition.

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Metabolic biomarkers of sleep and circadian disruption

Christopher Depner from the University of Utah presented work on developing metabolic biomarkers of sleep and circadian disruption. Depner hopes that a biomarker can provide a robust measure of circadian disruption for real-world studies. This can help bridge the rigorous controlled laboratory studies that link insufficient sleep to markers of metabolic dysfunction and the large epidemiologic studies that show associations between insufficient sleep and chronic metabolic diseases.[84–89]

Depner described his work using untargeted plasma metabolomics to identify small molecular biomarkers of circadian timing and insufficient sleep. In a randomized crossover study of healthy volunteers, participants completed 5-day conditions with 9- or 5-h time in bed sleep opportunities. Melatonin levels were measured hourly in dim-light conditions, with melatonin onset and offset used as a correlate for circadian timing. During the 9-h sleep condition, melatonin onset and offset were similar to that of the baseline, control period, while melatonin onset shifted approximately 2 h later during the 5-h sleep condition.[90] Statistically significant metabolomics-based biomarker models of melatonin onset and offset were developed. However, Depner stressed that the models need to be more robust for clinical settings. He believes that free access to food during the study may have confounded the ability to tease out the influence of sleep timing from food intake on these metabolomics-based biomarkers.[91] A separate study looking at transcription-based biomarkers has identified a more robust biomarker of circadian timing than Depner's metabolomics-based approach.[92]

Depner also used plasma metabolomics to identify biomarkers of insufficient sleep. A biomarker model of 65 metabolites showed 74% accuracy in identifying insufficient sleep among all samples and 80% accuracy among fasted samples, suggesting that food intake acutely impacted these metabolite leveles.[91] In fasted samples, biomarkers of insufficient sleep correlated with reduced insulin sensitivity. This is consistent with previous findings that show insulin sensitivity is reduced during insufficient sleep.[93] This correlation was lost, however, when controlling for body weight and energy balance, suggesting that the biomarker is impacted by positive energy balance and weight gain that occur during insufficient sleep. Depner is currently working to disentangle the impact of insufficient sleep from that of positive energy balance on the metabolome. He noted that it is important to think about the impact of food on sleep-related markers in real-world studies and stressed the need for trials that control food intake and monitor longer-term sleep trajectories.

Non-neuronal cells in sleep homeostasis: the role of astrocytes

Ashley Ingiosi from Washington State University presented work on understanding the role of astrocytes in regulating sleep. Even though glial cells are estimated to make up more than half of the cells in the brain, much less is known about their role in sleep compared with neurons. Ingiosi is specifically interested in glial cells called astrocytes. Several lines of evidence suggest that astrocytes can detect and integrate neural signals and alter neuronal activity; they surround synapses, interact with the neurovasculature, and express receptors for neurotransmitters.[94] Evidence also shows that astrocytes can influence sleep and sleep regulation[95–97] and that sleep deprivation can alter the astroglial proteome.[98]

Ingiosi investigated the role of astrocytes in sleep by monitoring astroglial Ca^{2+} activity in the frontal cortex of mice (Fig. 4). Unlike neurons, astrocytes are not electrically excitable cells. However, astrocytes use Ca^{2+} to mediate their functions, and previous studies showed that monitoring Ca^{2+} dynamics can be used to study astroglial activity.[99] In addition, astroglial Ca^{2+} has been shown to play a role in the release of sleep-promoting substances.[100] *In vivo* Ca^{2+} imaging of astrocytes in the frontal cortex of unanesthetized, freely behaving mice revealed that astroglial Ca^{2+} activity changed dynamically across naturally cycling sleep/wake states. Astroglial Ca^{2+} activity was aligned with neuronal EEG and electromyography determinations of arousal state. Ingiosi showed that astroglial Ca^{2+} activity was greatest during wakefulness and was lowest during rapid eye movement (REM) sleep. High-resolution two-photon microscopy showed that Ca^{2+} dynamics were more robust in the astroglial processes than in the cell body. In addition, the synchrony of astroglial Ca^{2+} activity was greatest during wakefulness, which differs from that of neuronal electrical activity, suggesting that astrocytes may play a more

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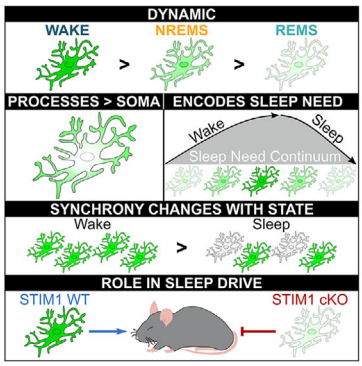
- Astrocytes represent a new level of brain organization that changes dynamically across arousal states
- Astroglial Ca^{2+} activity tracks changes in sleep need
- Synchrony of astroglial Ca^{2+} activity does not seem to mirror neuronal electrical activity
- Astroglial Ca^{2+} plays a role in regulating compensatory responses to sleep loss



Ingiosi et al., Curr Bio, 2020

Figure 4. **Astroglial Ca^{2+} activity contributes to sleep regulation.**

direct role in sleep/wake regulation than previously thought.

Ingiosi also showed that astroglial Ca^{2+} activity changed with sleep need and sleep deprivation. Astroglial Ca^{2+} activity was higher in sleepy mice compared with rested mice; this effect was more pronounced in sleep-deprived mice.[101]

Finally, Ingiosi showed that astroglial Ca^{2+} activity can impact sleep homeostasis. Inhibiting replenishment of astroglial Ca^{2+} stores through conditional knockout of stromal interaction molecule 1 (*Stim1*) in astrocytes impaired sleep deprivation-induced Ca^{2+} increases in astrocytes. After sleep deprivation, mice with impaired astroglial Ca^{2+} activity did not sleep as long as wild-type mice. They also displayed lower levels of sleepiness after sleep deprivation, as assessed by non-REM delta power. There was no impact of impaired astroglial Ca^{2+} activity on baseline sleep/wake behavior, activity patterns, or body temperature, which suggests that astroglial Ca^{2+} activity—as mediated by STIM1—plays a selective role in compensatory responses to sleep loss. Overall, Ingiosi proposed that astrocytes represent a new level of brain organization that changes dynamically across arousal states and plays a role in sleep homeostasis.[101]

High nighttime blood pressure and dementia risk

Blood pressure has a diurnal rhythm. Many people experience a 10–20% dip in blood pressure during the night and an increase in the morning after waking. Abnormalities in this diurnal pattern have been associated with CVD and cerebrovascular dysfunction. People who do not experience a nocturnal dip in blood pressure, known as nondippers, and people who experience a nightly rise in blood pressure, known as reverse dippers, are more likely to have hypertension and a higher risk of heart failure and stroke.[102] Reverse dipping is also associated with markers of small vessel cerebrovascular disease and impaired cognitive function in hypertensive individuals.[103]

Xiao Tan from Uppsala University presented work on the association between nighttime blood pressure and risk of dementia. Tan's work has investigated whether nondipping and reverse dipping are a risk factor for dementia. The study looked at approximately 1000 participants in the Uppsala Longitudinal Study of Adult Men, a cohort of 50-year-old men in Sweden that began in 1970. Average nighttime and daytime blood pressure values were measured in participants at ages 70 and 77 years. Tan showed that nocturnal blood pressure dipping decreased with age: 25% of 70-year-olds and 46% of 77-year-olds showed reduced dipping; reverse dipping was also associated with dementia risk. More specific, reverse dippers, that is, those who had higher blood pressure in the night compared with the day, had a 64% greater risk of dementia, in particular Alzheimer's disease. This effect was independent of hypertension or other common risk factors.[104] Tan noted that it may be worth investigating whether taking blood pressure medication in the evening, rather than earlier in the day, to lower nighttime blood pressure could lower the risk of dementia.

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There are a few possible mechanisms that can explain the link between high nocturnal blood pressure and Alzheimer's disease. First, given the link between reverse dipping and white matter hyperintensities,[93] high nighttime blood pressure may cause cerebrovascular injuries that may lead to white matter damage. Second, sleep disorders may play a role. A separate study has shown that 75% of reverse dippers also suffer from obstructive sleep apnea (OSA).[105] This could contribute to hypoxia in the brain, which may lead to accumulation of amyloid,[106] as well as increased arousal, which has been shown to increase tau protein.[107] Tan stressed that the diurnal pattern of blood pressure is often overlooked in clinical settings, where blood pressure is typically measured during the day. This could result in health problems going undetected.

The bidirectional relationship between nonapnea sleep disorders and stroke

Animal models have shown that sleep disruption can mediate both stroke risk and poststroke recovery.[108,109] Human studies on the relationship between sleep disruption and stroke have largely focused on sleep apnea; data on nonsleep apnea disorders are sparse.

Elie Gottlieb from the Florey Institute of Neuroscience and the University of Melbourne presented work aimed at understanding the bidirectional relationship between nonapnea sleep disorders and ischemic stroke. A systemic review by Gottlieb[110] examined the bidirectional relationship between nonapnea sleep and circadian rhythms in stroke patients. Sixty-seven studies with sleep or circadian rhythm metrics before or after stroke were included. Most prospective cohort studies reported a J-shaped relationship between sleep duration and stroke risk, though few studies adjusted for comorbidities like depression or OSA, which might be driving this relationship. In studies that examined the impact of nonapnea sleep disorders on ischemic stroke, sleep-related movement disorders, insomnia, REM behavior disorder, and hypersomnia were associated with increased risk of ischemic stroke. Studies that looked at sleep after stroke found that sleep efficiency decreased in the months following stroke, and patients experienced *de novo* sleep disorders. No studies assessed sleep for more than 1 year poststroke, so it is unclear whether these effects on sleep are transient and potentially related to hospitalization or if they are chronic. No studies assessed objectively measured circadian rhythm dysfunction on stroke risk; however, seven studies measured endogenous circadian rhythm poststroke. All reported significant reductions to melatonin relative to controls.

To try to understand the mechanism of sleep-related disorders after stroke, Gottlieb characterized regional brain volumes and fiber-specific white matter correlates of objectively measured sleep in 112 ischemic stroke patients and 40 matched controls. At 3 months after stroke, patients with long sleep duration showed cortico-ponto-cerebellar tract degeneration, which may be indicative of sleep/wake pathology. Stroke patients with normal sleep duration had extensive, diffuse white matter degeneration, which may be typical post-stroke and not related to sleep. Stroke patients with poor sleep efficiency also showed a decrease in ipsilesional thalamus volume and an increase in caudate volume (ipsilesional and contralateral) compared with matched controls.[111]

Gottlieb is currently conducting a long-term study with 4 years of follow-up to understand whether the sleep/wake impairments endured after stroke resolve over time.

Impact of the COVID-19 lockdowns on sleep

The COVID-19 lockdowns in the spring of 2020 brought about a sudden change in social behavior patterns and work schedules.

Christine Blume from the University of Basel presented her work on understanding the effect of the lockdowns on sleep quality, sleep behavior, social jetlag, and well-being via a one-time survey in three European countries (Austria, Germany, and Switzerland, 435 respondents) in March and April 2020. Overall, there was an improvement of the alignment between internal or biological and external or social rhythms. This was accompanied by a decrease in social jetlag, the difference in timing of sleep on work versus free days, and in social sleep restriction, the difference in sleep duration on work versus free days primarily driven by later and longer sleep time on work days. There was a median increase in sleep duration of approximately 13 minutes.[112] Other studies that have looked at the impact of the lockdowns

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on sleep with data available before and after the lockdown have likewise found increases in sleep time and decreases in social jetlag.[113,114]

Participants in Blume's study also reported a slight decrease in sleep quality. This was somewhat unexpected since aligning external and internal rhythms would be expected to increase sleep quality. However, the decrease in sleep quality was tied to the effects of the pandemic, as sleep quality was closely associated with self-perceived burden related to finances, childcare, and the pandemic situation. The decrease in sleep quality was partially mitigated in people who spent more time outside and exercised.[112] A separate study also reported a decrease in sleep quality due to the pandemic. In this study, people with poor sleep quality before the pandemic reported an improvement in sleep quality during the pandemic while those with good prepandemic sleep quality reported a decrease in sleep quality.[115]

Blume concluded that, overall, lockdowns had a positive effect on sleep timing and duration. Although sleep quality decreased, this was dependent on prepandemic sleep quality, and coping mechanisms like spending time outside and staying active may have mitigated these effects. While the effects of the pandemic represent a specific event that may prove to be short-lived, Blume hopes that studies like these can prompt broader discussions on how society can support good sleep, for example, by increasing flexibility in work schedules or adapting schedules to an individual's chronotype.

Conclusions

In modern societies, there is often a mismatch between the biological and social drivers that regulate sleep timing. This can lead to social jetlag (i.e., different sleep timing on work days and free days) and/or social sleep restriction (i.e., unequal sleep duration on work days and free days, often to compensate for sleep deficit during work days) and further influence timing of other behavioral patterns, such as eating. Sleep restriction, delayed eating, and social jetlag have been linked to negative health effects, such as depressive symptoms, poor performance at school/work, and chronic metabolic disease. In this symposium, experts in sleep and circadian rhythms have highlighted associations and demonstrated causal pathways linking sleep and circadian disruptions to disease risk. They have additionally recommended avenues for future research and potential applications for risk reduction and treatment. The meeting served as a preview to a future Keystone symposium (Sleep & Circadian Rhythms: Maintaining Tempo for Optimal Health) on the latest research in sleep and circadian rhythms to promote interactions and collaborative work in these overlapping fields.

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Competing interests

C. Benedict has served as a paid consultant to Repha GmbH, Langenhagen, Germany. C.V. serves on the scientific advisory boards of Circadian Lighting Inc., a Diabetes UK-funded study, and Chronsulting GmbH. C.V. has also served as a paid consultant to the DoE and NIOSH.

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