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Review

REVIEW

# Individual differences in light sensitivity affect sleep and circadian rhythms

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## Abstract

Artificial lighting is omnipresent in contemporary society with disruptive consequences for human sleep and circadian rhythms because of overexposure to light, particularly in the evening/night hours. Recent evidence shows large individual variations in circadian photosensitivity, such as melatonin suppression, due to artificial light exposure. Despite the emerging body of research indicating that the effects of light on sleep and circadian rhythms vary dramatically across individuals, recommendations for appropriate light exposure in real-life settings rarely consider such individual effects. This review addresses recently identified links among individual traits, for example, age, sex, chronotype, genetic haplotypes, and the effects of evening/night light on sleep and circadian hallmarks, based on human laboratory and field studies. Target biological mechanisms for individual differences in light sensitivity include differences occurring within the retina and downstream, such as the central circadian clock. This review also highlights that there are wide gaps of uncertainty, despite the growing awareness that individual differences shape the effects of evening/night light on sleep and circadian physiology. These include (1) why do certain individual traits differentially affect the influence of light on sleep and circadian rhythms; (2) what is the translational value of individual differences in light sensitivity in populations typically exposed to light at night, such as night shift workers; and (3) what is the magnitude of individual differences in light sensitivity in population-based studies? Collectively, the current findings provide strong support for considering individual differences when defining optimal lighting specifications, thus allowing for personalized lighting solutions that promote quality of life and health.

### Statement of Significance

This review integrates recent findings associating individual traits in humans, including age, sex, chronotype and genetic haplotypes, and the effect of evening/night light on sleep–wake regulation and circadian rhythms. Potential biological mechanisms for these individual differences in light sensitivity within the retina and downstream are discussed. Individuals in industrialized countries can spend up to ~90% per day indoors under artificial light, particularly in the evening/night hours, which negatively affects sleep and circadian physiology. Therefore, the current findings provide strong support for considering individual differences when designing optimal lighting specifications to benefit sleep and circadian rhythms. This will ultimately allow for successful personalized lighting solutions that foster better quality of life.

**Key words:** individual traits; light exposure; sleep–wake regulation; circadian rhythms; behavioral interventions

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## Introduction

Light is critical for human functioning as it confers the ability to see and perform activities [1]. Equally important, light influences human psychophysiology by inducing changes in neuroendocrine (e.g. melatonin suppression), sleep–wake quality, and psychological processes (e.g. subjective alertness) [2, 3]. Its broad range of action translates to a wide field of applications, ranging from optimizing work environments [4, 5] to behavioral treatments for patients with depression [6], patients with neurodegenerative diseases [7], to name a few. The contemporary world has seen a drastic change in the lighting landscape, with the common use of artificial light sources extending late into the night. Predictions based on data collected over the past decade suggest that ~10% of the world's land area shows artificial light at night [8], with numbers increasing to 23% if skyglow is included [9]. The "light at night" trend triggers profound effects on humans, as it sends mixed messages to the central circadian clock, which is evolutionarily tuned to the naturally recurring 24-h light–dark cycle [10]. Therefore, unintended overexposure to light in the evening/night hours can happen, which may result in decreased sleep quality. Emerging evidence indicates important individual differences in light sensitivity, such that typical indoor lighting may have negligible effects on circadian photosensitivity in one individual, whereas for another they may be exquisitely stronger [11]. However, recommendations for appropriate light exposure in real-life settings seldom consider such individual effects.

The goal of this narrative review is to provide an overview of recently identified individual variations in light sensitivity, including age, sex, chronotype and genetic haplotypes, and the effects of light exposure on sleep and circadian hallmarks. Studies described in this review come from human laboratory and field studies. As most studies used evening/night light exposure (therefore mimicking the effects of artificial light at night), this review focuses on light exposure at that time of day. Animal preclinical studies focusing on potential mechanisms for these light effects are not discussed at length, given this review's focus on human studies. Lastly, the review highlights the translational relevance of individual differences in light sensitivity to real-life settings (e.g. night shift work, adolescence) and in clinical populations typically exposed to artificial light at night (e.g. patients with delayed sleep–wake-phase disorder, individuals on the autism spectrum). Collectively, the reported findings reinforce the need to consider individual differences when defining lighting specifications for sleep and circadian rhythms, thus ensuring optimal, personalized lighting solutions.

## Effects of light on sleep–wake regulation and circadian rhythms

Circadian rhythms represent an evolutionary advantage, whereby the temporal organization of body functions harmonizes with the cyclic alterations of environmental stimuli [12]. Circadian rhythms require entrainment to the 24 h light–dark cycle, therefore rendering light as a critical modulator of sleep and circadian rhythms [13]. The effects of light occur during and/or immediately after exposure (acute effects) or after a given amount of time (long-term effects). Acute and long-term effects of light can bypass vision. Therefore, they are typically termed non-image-forming (NIF) effects of light. These effects are predominantly mediated via intrinsically photosensitive retinal ganglion cells (ipRGCs) [14], by activation of the photopigment melanopsin [15]. Importantly, the system mediating circadian photosensitivity (e.g. melatonin suppression) shows a spectral sensitivity consistent with that of melanopsin [16–18]. Melanopsin absorbs light in the short-wavelength range of the visible spectrum of light, with maximum sensitivity around 490 nm [19], after it passes through the cornea, lens, and ocular media (pre-receptoral filtering) [20]. While melanopsin is sufficient to drive NIF responses to light [21–23], some studies suggest the contribution of cones [16, 24]. Melanopsin-containing ipRGCs directly project to the suprachiasmatic nucleus (SCN, the circadian central pacemaker), through the retino-hypothalamic tract, and, directly or indirectly, to brain areas involved in sleep–wake regulation [25]. The SCN projects to the pineal gland, which regulates melatonin production [26]. This particular pathway accounts for the effects of light exposure on melatonin suppression and/or phase shifts of circadian melatonin rhythms.

Individuals exposed only to natural light–dark cycles, for example, in preindustrial societies [27] or in a naturalistic camping setup [28], show high daytime light levels, as they are mostly outdoors, and low evening light levels [27, 28]. In stark contrast, individuals living in industrialized societies are exposed to a profoundly altered light environment, with low natural daytime light levels, inadequate indoor daytime light, and high evening artificial light exposure (e.g. artificial room lighting, smartphones, and visual display units) [29]. Exposure to artificial light at night is predicted to increase by 3%–6% per year [30], with ~2% annual growth in radiance and extent [31], potentially increasing the likelihood of circadian disruption [32].

Circadian disruption is a disturbance of biological timing that happens at and/or between different organizational levels, and ranges from temporal disruption of molecular rhythms to the misalignment of behavioral cycles (e.g. sleep–wake cycles) with environmental changes [33, 34]. Circadian disruption may result in phase shifts of the circadian system, displacement of sleep relative to the central circadian pacemaker, and/or suppression of nocturnal melatonin production [2]. Evening/night exposure to light stimuli that provides greater melanopsin stimulation (for the same energy/photon flux/photopic illuminance) results in more melatonin suppression (e.g. blue-enriched vs. "standard" polychromatic or 460 nm vs. 550 nm) [16, 17, 24, 35–38], and in phase shifts of circadian melatonin rhythms [39–42]. Furthermore, it also reduces slow-wave activity during the first NREM–REM sleep cycle following light exposure [43, 44], which might be attributable to phase shifts of circadian melatonin rhythms.

A critical question that arises from these findings is whether some individuals are more sensitive to the effects of light on sleep and circadian rhythms. Albeit limited, emerging evidence suggests that individual differences in light sensitivity are very likely to be expected.

## One size does not fit all: individual differences in light sensitivity

Humans spend a substantial proportion of the day under moderate light intensities (~30–300 lx), particularly in the evening hours [45]. Individuals differ considerably in the

sensitivity and responsivity to environmental stimuli, with some being more and others less sensitive to a given environmental condition [46]. Hence, putative individual differences in light sensitivity to (for example) typical moderate light intensities may explain why some individuals show a heightened vulnerability to sleep and circadian disruption by artificial lighting. Recently, a within-subject human laboratory protocol assessed the impact of weekly evening polychromatic light exposures from low-to-high intensities (10–2,000 lx; 4.1–566 μW/cm$^2$) on melatonin suppression in young healthy men and women [11]. Approximately 50% of melatonin suppression were at light levels as low as <30 lx. Remarkably, a 50-fold range in light sensitivity occurred at the individual level, when comparing the least and most sensitive individuals. While some had more than 50% of acute melatonin suppression at ~10 lx (dim light), one required exposure to light at ~400 lx (bright light) for such response [11]. Similar findings were observed in a separate study with young healthy men exposed to 2 h of evening bright polychromatic light (1,000 lx) [47]. The degree of melatonin suppression by light was associated with (pharmacologically-dilated) pupil size during both pre-light exposure (dim light, 15 lx) and light exposure [47]. Therefore, baseline pupil size may be a predictor of individual differences in circadian photosensitivity. Moreover, sensitivity to light depends on photic history, as shown in a randomized crossover study with healthy young men and women who underwent two illuminance histories (1 lx vs. 90 lx) before a 6.5 h 90 lx light stimulus at night [48]. Waking EEG activity in the delta/theta range (2.0–5.5 Hz range) during the 6.5 h light exposure was lower when individuals were exposed to prior illuminance of 1 lx than exposed to 90 lx [48]. The influence of photic history is shown in a functional magnetic resonance imaging (fMRI) study with healthy young men and women [49]. The influence of a test light (515 nm) on executive brain responses depended on the light wavelength to which individuals were exposed to 1 h before. When they were exposed to long-wavelength light (589 nm), but not short-wavelength (461 nm), widespread activations in prefrontal areas and in the pulvinar occurred during a simple auditory detection task and a more difficult auditory working memory task [49]. While there are no reported studies on individual differences in photic history, such variability is likely to exist.

Differences in circadian photosensitivity occur when individuals are exposed to long-term evening artificial light [50]. Young healthy men and women exposed to 6–8 weeks of bright polychromatic evening light at home followed by a laboratory protocol showed large individual differences in melatonin suppression by light [50]. These findings suggest that some individuals are more vulnerable to long-term adverse effects of evening light exposure and, therefore, may be at higher risk of circadian disruption. This assumption is tentatively supported by an association of individual differences in melatonin suppression and the activation of a suprachiasmatic area in a human fMRI study [51]. Ten healthy young men and women underwent evening exposure to dim light (<10 lx) followed by moderate intensity polychromatic white light (100 lx, 2,800 K, irradiance: 42.73 μW/cm$^2$) [51]. Individuals with increased melatonin suppression also had an increased activation within a suprachiasmatic area in response to the light exposure. Yet, it is unclear whether individual differences in photic input, SCN function, and/or nonretinal input to the SCN in response to light modulate individual variability in circadian photosensitivity. Evidence of differences in photic input builds from individual differences in sustained pupil responses to light (polychromatic white light at ~150 lx for 6.5 h) in patients with delayed sleep–wake-phase disorder [52]. Evidence of differences in nonretinal input to the SCN comes from a within-subject study with healthy young men and women who had evening polychromatic light exposure (~100 lx) combined with a single dose of citalopram 30 mg (selective serotonin reuptake inhibitors, SSRIs) or placebo [53]. The large effect size for melatonin suppression by light with citalopram intake suggests that individual variability in raphe input to the SCN (a target region for SSRIs action) might contribute to differences in light sensitivity.

Which individual traits underlie the effects of light on sleep and circadian rhythms? Developmental age, sex, chronotype, and genetic haplotypes are traits that may explain the heightened vulnerability experienced by some individuals (see Figure 1 for a conceptual scheme). Healthy aging (individuals above 55 years) is perhaps the most studied individual trait for light sensitivity to date, with evidence of reduced sensitivity to short-wavelength light on circadian photosensitivity [40, 54]. Older individuals can exhibit attenuated melatonin suppression by light at short-wavelength (~480 nm) rather than at long-wavelength (~550 nm), as compared to young individuals [54]. Moreover, older individuals may show a shift of NIF light sensitivity ($\lambda_{max}$ = 494 nm), as compared to young individuals ($\lambda_{max}$ = 484 nm) [55]. However, melatonin suppression in response to short-wavelength light (<500 nm) was similar in young and older individuals in that same study [55]. Healthy aging may not necessarily affect the phase-shifting response to polychromatic light exposure, with similar phase shifts in circadian melatonin rhythms between young and older individuals [40, 56, 57]. Therefore, some aspects of circadian photosensitivity can be preserved with advancing age. In young individuals, robust carryover alerting responses of short-wavelength light can influence sleep physiology (e.g. longer sleep latency, altered slow-wave activity dynamics) [35, 43, 44]. Conversely, findings on the effects of light on sleep in older individuals are limited [58, 59]. A 40-h sleep deprivation paradigm with exposure to either polychromatic light at 250 lx (2,800 K), polychromatic light at 250 lx (9,000 K) or dim light at 8 lx (2,800 K) showed increased slow-wave activity in both young and older individuals during sleep recovery [58]. Therefore, under challenging conditions, the sleep homeostatic response to light exposure maybe conserved with advancing age. Another study investigated the effects of evening light exposure in older individuals with sleep complaints [59]. After 3 baseline days, participants underwent 2 h of acute polychromatic white fluorescent light (4,100 K) or blue-enriched polychromatic white fluorescent light of equal photon density (1.E+15 photons/cm$^2$/s) [59]. REM sleep latency increased following exposure to both light settings, probably due to a phase delay of 1 h in circadian melatonin rhythms (although there was no significant association between these outcomes).

Healthy aging is associated with a progressive decrease in light transmission due to the clouding and yellowing of the natural crystalline lens [60], especially for short-wavelength light [61]. Importantly, these age-related effects within the eye may adversely influence sleep quality [62]. Older individuals may also have reduced pupil size [63] and lens transmittance [55], and increased ocular lens absorption [64]. Thus, older individuals

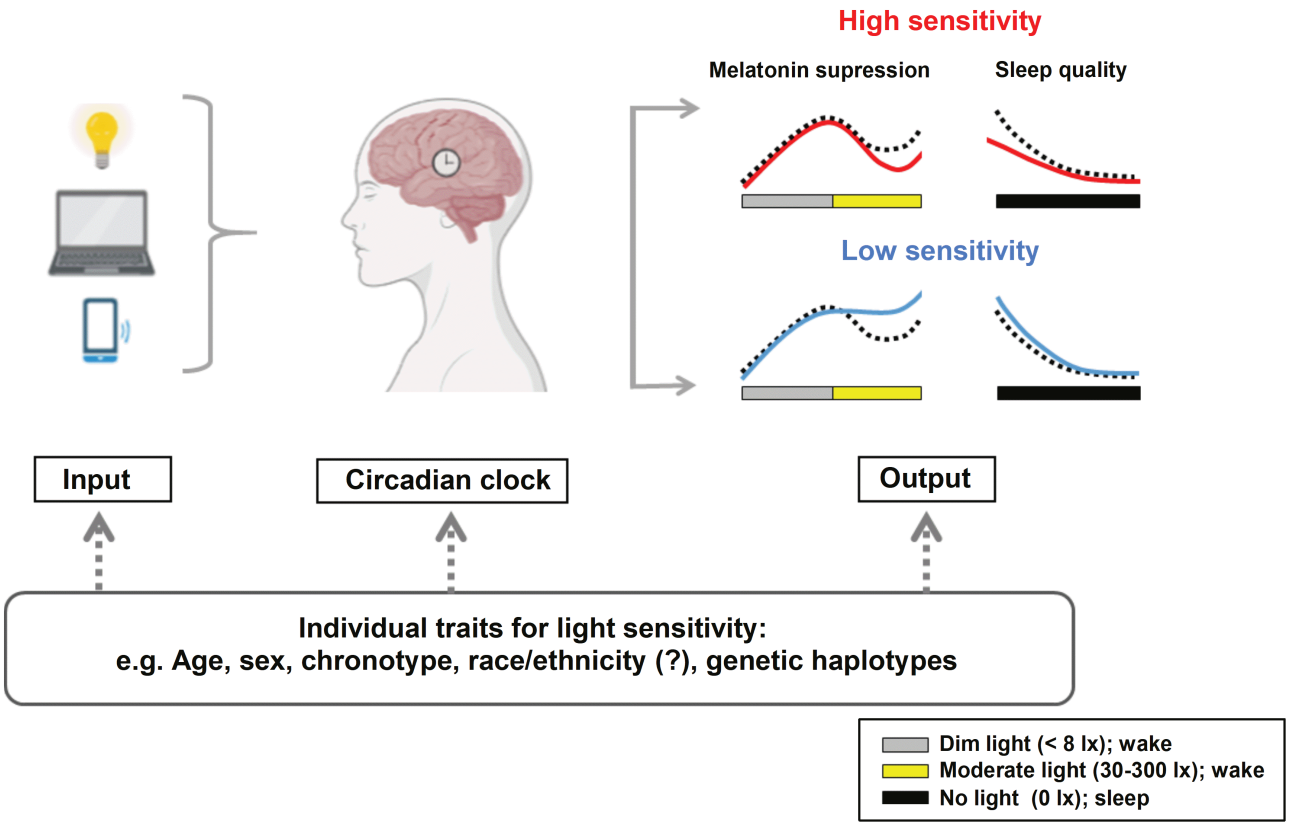


**Figure 1.** Conceptual scheme of individual differences in light sensitivity effects on sleep and circadian rhythms. Photic input, through, for example, light bulbs and electronic devices, impinge onto the human SCN (central circadian clock) [12], resulting in a multitude of NIF responses to light (output) [2, 13]. Recent evidence shows individual differences in circadian photosensitivity [11]. High sensitivity leads to increased melatonin suppression by evening/night light exposure (red line), as compared to the group average (dashed black line). In contrast, low sensitivity leads to minimal (if any) melatonin suppression by evening/night light exposure (blue line), as compared to the group average (dashed black line). Although not fully established, similar individual differences in light sensitivity are expected to occur for sleep quality (here, indexed as e.g. slow-wave activity, 0.75–4.5 Hz). Accordingly, high sensitivity may result in less slow-wave activity, particularly at the beginning of the sleep episode, subsequent to evening/night light exposure (red line), as compared to the group average (dashed black line). In contrast, low sensitivity may result in minimal (if any) effects of evening/night light exposure on slow-wave activity (blue line), as compared to the group average (dashed black line). Such individual differences in light sensitivity may be ascribed to a constellation of traits, including age, sex, chronotype, and genetic haplotypes (e.g. [42, 55, 56, 68, 69, 79, 89, 90, 96]). Albeit race/ethnicity influences sleep/circadian rhythms, there are currently no studies on this trait as mediating the effects of light exposure. Individual traits may influence the effects of light on sleep and circadian rhythms at the level of the eye (input) and/or downstream (circadian clock and beyond). Dashed lines to input, circadian clock and to output indicate that potential mechanisms are known for some individual traits, but not all (e.g. [3, 52, 53]).

may experience reduced photic input, with downstream sleep and circadian disruption. Age-related cataracts further worsen these ocular processes and are associated with disrupted sleep and circadian rhythms [65]. However, when patients with cataract undergo intraocular lens replacement (ultraviolet-only blocking or blue-blocking [BB] lens), they show increased melatonin sensitivity to 2 h of acute evening polychromatic light (~40 lx, 2,500 K, and 6,000 K) by ~27%, as compared to healthy older individuals [66]. Patients with ultraviolet-only blocking lens replacement show improved sleep (e.g. longer slow-wave sleep duration by ~8% [66]), as compared to healthy controls. Moreover, the same patients with ultraviolet-only blocking lens replacement show better cognitive performance (e.g. sustained attention [66] and procedural learning [67]), as compared the patients with BB lens. These findings suggest that optimizing the spectral lens transmission in patients with cataract may improve circadian photosensitivity, sleep, and cognitive function.

Individual differences in light sensitivity also occur at earlier developmental stages. Two studies have hypothesized that melatonin suppression by light is larger in children, as compared to adults, since they have large pupils and pure crystal lenses [68, 69]. In the first study, healthy young primary school children and healthy adults underwent two light experiments [68]. In one protocol, they had low (dim) light (<30 lx) and moderately bright polychromatic white light (580 lx). In the other protocol, they had a similar dim light condition and light exposure at moderate indoor levels (~140 lx). In both laboratory protocols, children had almost twice the percentage of melatonin suppression by light as compared to adults, indicating increased circadian photosensitivity. In the second study, healthy children and adults underwent two sets of ~4 h evening light experiments with dim light followed by polychromatic light at 3,000 K or at 6,200 K (melanopic illuminance: 149.2 and 292.9 m-lx, respectively, with matched photon density [14.4 log photons/cm$^2$/s]) [69]. Melatonin suppression in children was greater as compared to adults, particularly for light at 6,200 K (higher melanopic illuminance). Similarly, the effects of 1 h evening acute light exposure at different intensities (0.1, 15, 150, and 500 lx) on melatonin levels differed between the developmental groups [70]. Pre- to mid-pubertal individuals (9–14 years) had greater melatonin suppression by light, as compared to late- to postpubertal adolescents (11.5–16 years) [70]. Therefore,

exposure to evening light can be very disruptive for children, which is problematic as they increasingly use artificial lighting (e.g. TV screens, computer games, and smartphones) [71], and can experience adverse effects on their sleep patterns [72].

Sleep and circadian rhythms display race/ethnicity differences [73]. African-Americans as compared to European-Americans show a shorter circadian period by 0.2 h [74], are less likely to show phase delays as a response to a 9-h phase-shifting circadian protocol [75], and show more sleep disruption because of circadian misalignment [76]. However, individual differences in light sensitivity may confound these circadian period and phase assessments, as participants remained under ~35 lx, and recent evidence indicates individual differences unless light levels are very dim (<10 lx) [11]. Furthermore, in the UK Biobank dataset (439,933 individuals), black participants had twice the prevalence of short sleep duration (5–6 h) and were 1.4-fold more likely to be morning types [77]. Despite these differences, there is very limited research on race/ethnicity as an individual trait for light sensitivity, with a single study on the influence of eye colors between Caucasians and Asians on melatonin suppression by light [78].

There is some indication for sex-dependent effects of light in humans [79]. Exposure to 2 h of evening polychromatic light (~40 lx) at 6,500 K or at 2,500 K may affect brightness perception, vigilant attention, and sleep in a sex-dependent manner. While no sex differences occurred for melatonin suppression by light, men had increased subjective perception of brightness and all-night frontal slow-wave activity at the beginning of the sleep episode following exposure to light at 6,500 K [79]. Importantly, because the young men also had better sustained attention performance during the acute light exposure, the subsequent increased slow-wave activity might reflect a use-dependent phenomenon [79]. The sex-dependent sensitivity to light could be due to differences in visual system function [80]: primary visual cortex responses to stepped intensities of red and blue light show twofold higher stimulus-response curves for men, as compared to women. However, further studies with larger sample sizes are required to establish an association of sex and light sensitivity.

A key individual trait of light sensitivity is chronotype, which is the propensity for an individual to sleep and wake-up at specific times within a 24-h day, resulting in earlier, intermediate, and later chronotypes with temporal niches separated by as much as 10 h [81]. Currently, there are no controlled laboratory studies that have compared the effects of artificial light on sleep and circadian rhythms among earlier, intermediate, and later chronotypes. Field studies show increased light exposure during the day is associated with an earlier chronotype in the general population [82–84]. Therefore, chronotype may mediate the effects of light on sleep and circadian rhythms. Genetic haplotypes are likely candidates for individual differences in light sensitivity. Variations in circadian clock genes (e.g. *PERIOD2*, *CLOCK*, and *casein kinase 1 epsilon*) are associated with human sleep and circadian disorders [85, 86], including familial advanced sleep phase syndrome [85]. *PERIOD* (*PER*) genes are essential factors contributing to circadian clock gene regulation [87] and therefore potential candidates for the effects of light exposure on sleep and circadian rhythms. The association of circadian photosensitivity and genetic haplotypes is highlighted in a study, whereby young men and women were exposed to 4 h of dim light (<15 lx) followed by bright polychromatic light (1,000 lx, 5,000 K) [88]. *PER2* haplotype homozygosity accounted for a low sensitivity to light, as indexed by lower percentage of acute melatonin suppression by 3 h of evening polychromatic bright light (1,000 lx measured at participant eye level). Furthermore, individual differences in NIF responses to light on sleep phenotypes may depend on specific genetic traits (*PER3* variable-number tandem repeat [VNTR] polymorphism) also involved in sleep–wake regulation. When young men homozygous to the longer variant of the *PER3* VNTR polymorphism had 2 h of evening polychromatic light at 6,500 K or at 2,500 K (~40 lx), they had more melatonin suppression by light at 6,500 K, as compared to individuals with the shorter *PER3* variant [89], and more slow-wave activity in the occipital cortex [90]. Similar heightened light sensitivity (to 427 nm vs. 527 nm wavelength light exposure) is observed for cognitive brain function following ~25 h of sleep deprivation in individuals with the longer *PER3* variant [91]. Genetic variants of the human melanopsin gene (*OPN4*) associate with sleep–wake timings [92], such that individuals with CC genotype of the *OPN4*Ile394Thr* variant show later timings than those with the TT or TC genotype. Furthermore, the human missense *OPN4* gene can mediate the risk of seasonal affective disorder [93]. The naturally occurring missense variants in the human *OPN4* gene may result in melanopsin proteins with a significant loss-of-function phenotype, potentially increasing the likelihood of visual deficits, sleep, and circadian disruption [94].

## Role of individual traits on sleep and circadian rhythms

Likely candidates for individual differences in light sensitivity include individual differences in sleep and circadian rhythms, such as age, sex, chronotype, race/ethnicity, and genetic haplotypes. Sleep and circadian rhythms change over lifespan, such that already at adolescence, there is a delay in sleep timing, and a gradual reduction in slow-wave sleep [95, 96]. With advancing age, sleep timing advances, and sleep consolidation, sleep duration and slow-wave sleep decrease, irrespective of circadian phase [95–97]. These age-related changes presumably involve alterations in sleep architecture and sleep propensity, and in circadian rhythms, such as decreased amplitude of the circadian wake-propensity rhythm and melatonin secretion at night [97]. Sex-dependent differences also occur in sleep, with women exhibiting more slow-wave activity at dim light melatonin onset (DLMO; i.e. typically close to habitual bedtime), particularly in centro-parietal brain regions [98]. Moreover, women may have shorter average intrinsic circadian period [99], higher amplitude of melatonin rhythms and lower amplitude of core body temperature (CBT) rhythms, and earlier timing of melatonin and CBT rhythms relative to sleep time [100].

With respect to chronotype, earlier as compared to later chronotypes show advanced circadian phase (e.g. earlier DLMO), and higher initial levels and decay rate of slow-wave activity [101, 102]. Furthermore, chronotype depends on sex and age: men are later chronotypes as compared to women before 40 years, reversing to earlier chronotypes afterwards; and latest sleep timings occur in adolescents, whereas the earliest occur in older individuals [103]. Genetic variants also play a crucial role in individual differences in sleep and circadian rhythms,

with reported associations of candidate circadian gene variants (i.e. *PER2* and *PER3* polymorphisms) and homeostatic sleep EEG hallmarks [104, 105]. Furthermore, genome-wide association studies in adults of European ancestry identified 78 loci for self-reported habitual sleep duration [106], accelerometer-derived sleep duration, sleep efficiency and number of sleep bouts [106], and that the chronotype loci associates with sleep timing [107]. Collectively, individual traits of specific sleep and circadian phenotypes may partly explain the individual variability in light sensitivity.

## Translational relevance of individual differences in light sensitivity

Adapting artificial evening/night light exposure to individual vulnerabilities may minimize the increased likelihood of sleep and circadian disruption experienced by some individuals, such as night shift workers. Shift work is a risk factor for cardiometabolic diseases, and key players involved in these adverse health effects include artificial light at night, circadian misalignment, and sleep restriction or deprivation [108]. Circadian rhythms of shift workers undergo, at least to some extent, phase adjustments after a change in work schedule [109]. Light exposure at the latter part of the circadian night (as in backward [night-to-day] rotating shift work schedule) may phase advance circadian rhythms [109]. Conversely, light exposure at the early part of the night (as in forward [day-to-evening/night] rotating shift work schedule) may phase delay circadian rhythms [109]. Importantly, factors determining resilience or vulnerability to shift work schedules include direction of the circadian phase shift, type of work schedule, and individual susceptibility to artificial light exposure [110, 111]. Recently, a field study identified the 24 h light-dark profiles measured with ambient light data loggers in day or night shifts of 100 women, and showed differences in light exposure among shift work schedules [112]. Night work reduced the duration of darkness per day by almost 4 h (particularly during the winter), and later chronotypes had higher light exposure in the morning and evening, as compared to intermediate chronotype. These results are in contrast to a previous study that did not report significant differences in light exposure among chronotypes and shift work schedules of 39 police officers [113]. Discrepancies between these studies may include differences in sample size, sex distribution, and analyses of hourly light intensities versus overall 24 h light profiles. Thus, individual traits as sex and chronotype, may partly explain why some individuals who perform shift work have an increased risk of sleep and circadian disruption.

One particular chapter in developmental age that is receiving growing interest in the light field is adolescence. A recent population-based, cross-sectional study of US adolescents showed higher artificial light at night levels (highest quartile of outdoor levels) were associated with later weeknight bedtime (~30 min difference), shorter sleep duration (~10 min difference), and increased risk of mood and anxiety disorders [114]. Adolescents often expose themselves to more indoor lighting (e.g. computers, tablets, and smartphones) before bedtime [115]. Data from a field study suggest an association of frequent electronic device usage and increased sleep problems in adolescents [116]. Laboratory data also show differences in light sensitivity between adolescents and adults [117]. Accordingly, adolescents (but not adults) show more melatonin suppression after 4 h of evening exposure to polychromatic light at 5,600 K (209 lx) than at 2,700 K (295 lx), despite equal photon density [117]. Furthermore, when male adolescents wore BB glasses in front of a light-emitting diode (LED) computer screen in the evening, they had reduced melatonin suppression and subjective alertness, but no changes in sleep stages, as compared to when they wore control glasses [118]. Despite the limited sample size and the inclusion of only male adolescents, this study suggests that BB glasses might aid adolescents against the adverse effects of light exposure on circadian photosensitivity during the evening/night hours.

The translational relevance of individual differences in light sensitivity extends to clinical populations who are at a higher risk of exposure to artificial light at night. Patients with delayed sleep–wake phase disorder (DSWPD) show heightened circadian photosensitivity, as compared to healthy young individuals [52]. When exposed to 6.5 h of nocturnal polychromatic light (150 lx, irradiance: 44.83 μW $cm^{-2}$), patients with DSWPD showed 31.5% greater phase delay shifts, as compared to healthy young individuals. Therefore, individual light sensitivity recommendations for behavioral interventions are needed for this population. Recent evidence indicates that individuals on the autism spectrum frequently experience altered light sensitivity [119]. Autism spectrum is an early onset neurodevelopmental condition often associated with sensory processing disorders. Bright lighting, in addition to a sensory overloaded environment, may provoke strong or painful responses to light, hindering the ability to adequately process light stimuli in individuals with autism spectrum [120]. Importantly, they often report sleep difficulties, including reduced total sleep time, delayed sleep onset, and increased nocturnal awakenings [121], which may improve following 3 months of daily exogenous melatonin (5 mg) intake [122]. The sleep and circadian disruption often experienced by individuals on the autism spectrum can partially worsen because of the excessive use of electronic devices at night, to which they are particularly drawn [123]. Children on the autism spectrum show stronger sensitivity to evening light exposure on the sleep (e.g. greater sleep onset delay, shorter sleep duration), as compared to children with typical neurodevelopment [123]. Thus, optimal adaptation of the timing and type of light exposure in the evening/night hours is necessary for these individuals.

## Concluding remarks and future perspectives

Light is essential for human productivity, safety, and health. More often than not, we rely on artificial light. However, the current overexposure to artificial light, particularly at night, can adversely affect human health with unintended disruption of sleep and circadian rhythms [124]. While there is growing awareness of reducing evening/night light exposure, recommendations for appropriate light exposure are based on group-level effects. This review discussed a shifting paradigm in the human light field: the acknowledgment that people do not respond the same way to the same light exposure. The assessment of individual differences in photosensitivity builds from human laboratory and field studies (Figure 2). The former allows identifying individual photosensitivity based

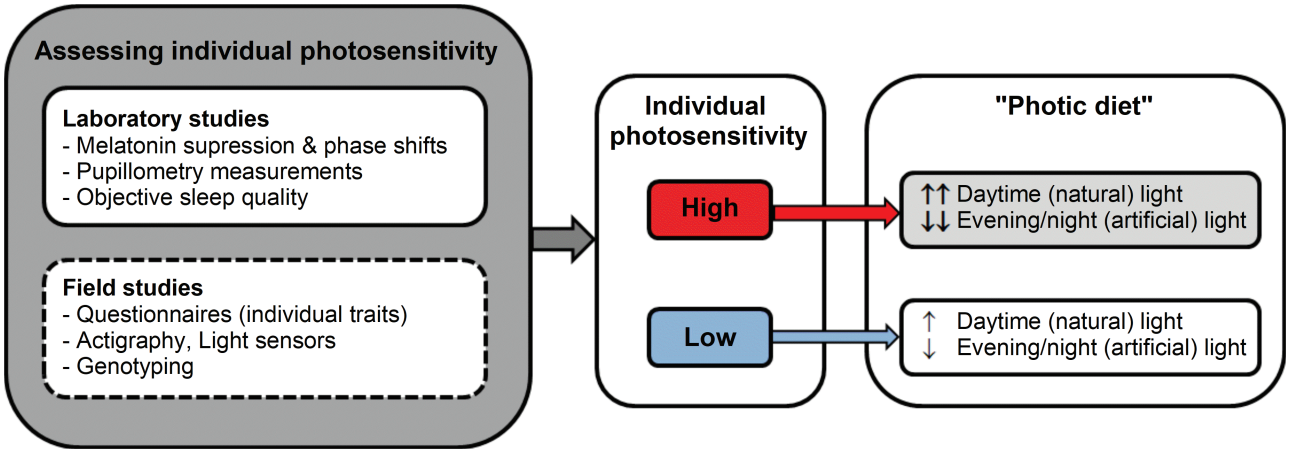


**Figure 2.** Assessing individual photosensitivity for potential personalized lighting recommendations. Assessment of individual photosensitivity in humans has come from human laboratory and field studies, which use different outcome measures to index sleep and circadian rhythms. By identifying individuals with high or low sensitivity to light, a potential "light diet" tailored to individual needs might become feasible (see text for detailed discussion).

on well-established hallmarks of sleep and circadian rhythmicity. These include light-induced melatonin suppression and phase shifts of circadian melatonin rhythms, pupillometry measurements (associated with the acute melatonin suppression by light), and objective sleep quality (e.g. slow-wave activity). Field studies help identifying individual photosensitivity through screening questionnaires assessing individual traits linked to light sensitivity, such as age, sex, chronotype, race/ethnicity, genetic haplotypes and other factors (e.g. season when studies occurred). Wrist-worn actigraphy measurements combined with sleep diaries and light sensors allow determining real-life sleep quality measurements, circadian/sleep stability, and daily light patterns [125]. Given the identification of individuals with low or high light sensitivity, specific recommendations for a "light diet" might be possible. For instance, individuals with high light sensitivity could be prescribed more daytime (natural) light and low evening/night melanopic lx light exposure. Conversely, individuals with low sensitivity could be prescribed similar—albeit less stringent—light recommendations. Recent human laboratory evidence also shows that dynamically changing daylight LED light exposure may benefit circadian photosensitivity and sleep quality [126]. In that laboratory protocol, healthy men and women underwent either static daylight LED (100 lx, 4,000 K) or dynamic daylight LED that changed color (0–100 lx, 2,700–5,000 K) across 16 h of scheduled wakefulness. Evening melatonin levels were less suppressed ~1.5 h before habitual bedtime and sleep latency was shorter under dynamic light as compared to static light. Although results are shown at the group level, it is possible that individual adaptation of dynamic lighting solutions will benefit sleep and circadian rhythms for individuals with high light sensitivity.

While promising and exciting, further research is required to determine the individual variability to light sensitivity. For instance, most human studies have used laboratory protocols in the evening/night hours. However, we know little about individual differences in daytime light exposure, as certain aspects of daytime (natural) light cannot be effortlessly mimicked by artificial light, including seasonal changes in day length or twilight conditions (for a comprehensive review, see [127]). This is important, as appropriate light recommendations for day/night shift workers with altered light profiles require considering light within and outside their workplace. Another important question is the magnitude of individual differences in light sensitivity effects, that is, the effect size of different individual traits mediating the effects of light on sleep and circadian rhythms. The human laboratory and field studies that have helped to establish a role of these individual traits have limited sample sizes, due to their inherent study design complexity and the stringent inclusion/exclusion study participant criteria. Therefore, population-based studies may help to capture relevant light exposure differences across individuals, as well as potential collinearities among these individual traits. The challenge for population-based studies, however, includes a lack of consensus on practical assessments for monitoring real-life day and night light exposure over months and years. The use of wearable, validated sleep and circadian technologies that involve multisystem data collection with multisensory and/or accelerometer-based generation devices [128] may provide some alternatives. Lastly, as artificial light exposure is an everyday occurrence in contemporary lives, it is pivotal to identify individual differences in *long-term* effects of light on sleep and circadian rhythms. Ultimately, this will allow for personalized light solutions in real-life, which will require a trade-off between feasible costs and realistic strategies that can account for individual differences in light sensitivity moving forward.

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## References


1. Boyce P, *et al*. *The Benefits of Daylight Through Windows*. Troy, NY: Rensselaer Polytechnic Institute; 2003.
2. Chellappa SL, *et al*. Can light make us bright? Effects of light on cognition and sleep. *Prog Brain Res*. 2011;**190**:119–133.
3. Prayag AS, *et al*. Light modulation of human clocks, wake, and sleep. *Clocks Sleep*. 2019;**1**(1):193–208.
4. Horowitz TS, *et al*. Efficacy of bright light and sleep/darkness scheduling in alleviating circadian maladaptation to night work. *Am J Physiol Endocrinol Metab*. 2001;**281**(2):E384–E391.
5. Viola AU, *et al*. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand J Work Environ Health*. 2008;**34**(4):297–306.
6. Lam RW, *et al*. Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*. 2016;**73**(1):56–63.
7. Riemersma-van der Lek RF, *et al*. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA*. 2008;**299**(22):2642–2655.
8. Gaston KJ, *et al*. Human alteration of natural light cycles: causes and ecological consequences. *Oecologia*. 2014;**176**(4):917–931.
9. Falchi F, *et al*. The new world atlas of artificial night sky brightness. *Sci Adv*. 2016;**2**(6):e1600377.
10. Stevens RG, Zhu Y. Electric light, particularly at night, disrupts human circadian rhythmicity: is that a problem? *Philos Trans R Soc Lond B Biol Sci*. 2015;**370**(1667).
11. Phillips AJK, *et al*. High sensitivity and interindividual variability in the response of the human circadian system to evening light. *Proc Natl Acad Sci USA*. 2019;**116**(24):12019–12024.
12. Moore RY. Circadian rhythms: basic neurobiology and clinical applications. *Annu Rev Med*. 1997;**48**:253–266.
13. Cajochen C, *et al*. What keeps us awake? The role of clocks and hourglasses, light, and melatonin. *Int Rev Neurobiol*. 2010;**93**:57–90.
14. Berson DM, *et al*. Phototransduction by retinal ganglion cells that set the circadian clock. *Science*. 2002;**295**(5557):1070–1073.
15. Hattar S, *et al*. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*. 2002;**295**(5557):1065–1070.
16. Thapan K, *et al*. An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *J Physiol*. 2001;**535**(Pt 1):261–267.
17. Brainard GC, *et al*. Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci*. 2001;**21**(16):6405–6412.
18. Prayag AS, *et al*. Melatonin suppression is exquisitely sensitive to light and primarily driven by melanopsin in humans. *J Pineal Res*. 2019;**66**(4):e12562.
19. Wright HR, *et al*. Effect of light wavelength on suppression and phase delay of the melatonin rhythm. *Chronobiol Int*. 2001;**18**(5):801–808.
20. Spitschan M. Melanopsin contributions to non-visual and visual function. *Curr Opin Behav Sci*. 2019;**30**:67–72.
21. Souman JL, *et al*. Spectral tuning of white light allows for strong reduction in melatonin suppression without changing illumination level or color temperature. *J Biol Rhythms*. 2018;**33**(4):420–431.
22. Allen AE, *et al*. Exploiting metamerism to regulate the impact of a visual display on alertness and melatonin suppression independent of visual appearance. *Sleep*. 2018;**41**(8). doi: 10.1093/sleep/zsy100.
23. Zaidi FH, *et al*. Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. *Curr Biol*. 2007;**17**(24):2122–2128.
24. Gooley JJ, *et al*. Spectral responses of the human circadian system depend on the irradiance and duration of exposure to light. *Sci Transl Med*. 2010;**2**(31):31ra33.
25. Gooley JJ, *et al*. A broad role for melanopsin in nonvisual photoreception. *J Neurosci*. 2003;**23**(18):7093–7106.
26. Lockley SW, *et al*. Circadian photoreception: spotlight on the brain. *Curr Biol*. 2006;**16**(18):R795–R797.
27. Yetish G, *et al*. Natural sleep and its seasonal variations in three pre-industrial societies. *Curr Biol*. 2015;**25**(21):2862–2868.
28. Wright KP Jr, *et al*. Entrainment of the human circadian clock to the natural light-dark cycle. *Curr Biol*. 2013;**23**(16):1554–1558.
29. Irwin A. The dark side of light: how artificial lighting is harming the natural world. *Nature*. 2018;**553**(7688):268–270.
30. Hölker F, *et al*. The dark side of light: a transdisciplinary research agenda for light. *Ecol Soc*. 2010;**15**:13.
31. Kyba CCM, *et al*. Artificially lit surface of Earth at night increasing in radiance and extent. *Sci Adv*. 2017;**3**(11):e1701528.
32. Tähkämö L, *et al*. Systematic review of light exposure impact on human circadian rhythm. *Chronobiol Int*. 2019;**36**(2):151–170.
33. Qian J, *et al*. Circadian system and glucose metabolism: implications for physiology and disease. *Trends Endocrinol Metab*. 2016;**27**(5):282–293.
34. Vetter C. Circadian disruption: what do we actually mean? *Eur J Neurosci*. 2020;**51**(1):531–550.
35. Chang AM, *et al*. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proc Natl Acad Sci USA*. 2015;**112**(4):1232–1237.
36. Chellappa SL, *et al*. Non-visual effects of light on melatonin, alertness and cognitive performance: can blue-enriched light keep us alert? *PLoS One*. 2011;**6**(1):e16429.
37. Cajochen C, *et al*. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. *J Appl Physiol (1985)*. 2011;**110**(5):1432–1438.
38. Najjar RP, *et al*. Temporal integration of light flashes by the human circadian system. *J Clin Invest*. 2016;**126**(3):938–947.
39. Zeitzer JM, *et al*. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol*. 2000;**526**(Pt 3):695–702.
40. Sletten TL, *et al*. Age-related changes in acute and phase-advancing responses to monochromatic light. *J Biol Rhythms*. 2009;**24**(1):73–84.
41. Appleman K, *et al*. Controlling light-dark exposure patterns rather than sleep schedules determines circadian phase. *Sleep Med*. 2013;**14**(5):456–461.
42. Figueiro MG, *et al*. The effects of chronotype, sleep schedule and light/dark pattern exposures on circadian phase. *Sleep Med*. 2014;**15**(12):1554–1564.
43. Chellappa SL, *et al*. Acute exposure to evening blue-enriched light impacts on human sleep. *J Sleep Res*. 2013;**22**(5):573–580.
44. Münch M, *et al*. Wavelength-dependent effects of evening light exposure on sleep architecture and sleep EEG power density in men. *Am J Physiol Regul Integr Comp Physiol*. 2006;**290**(5):R1421–R1428.
45. Münch M, *et al*. Light and chronobiology: implications for health and disease. *Dialogues Clin Neurosci*. 2012;**14**(4):448–453.
46. de Villiers B, *et al*. Vantage sensitivity: a framework for individual differences in response to psychological intervention. *Soc Psychiatry Psychiatr Epidemiol*. 2018;**53**(6):545–554.

47. Higuchi S, *et al*. Inter-individual difference in pupil size correlates to suppression of melatonin by exposure to light. *Neurosci Lett*. 2008;**440**(1):23–26.
48. Chang AM, *et al*. Direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans depend on prior light history. *Sleep*. 2013;**36**(8):1239–1246.
49. Chellappa SL, *et al*. Photic memory for executive brain responses. *Proc Natl Acad Sci USA*. 2014;**111**(16):6087–6091.
50. Santhi N, *et al*. The spectral composition of evening light and individual differences in the suppression of melatonin and delay of sleep in humans. *J Pineal Res*. 2012;**53**(1):47–59.
51. McGlashan EM, *et al*. Imaging individual differences in the response of the human suprachiasmatic area to light. *Front Neurol*. 2018;**9**:1022.
52. Watson LA, *et al*. Increased sensitivity of the circadian system to light in delayed sleep-wake phase disorder. *J Physiol*. 2018;**596**(24):6249–6261.
53. McGlashan EM, *et al*. The SSRI citalopram increases the sensitivity of the human circadian system to light in an acute dose. *Psychopharmacology (Berl)*. 2018;**235**(11):3201–3209.
54. Herljevic M, *et al*. Light-induced melatonin suppression: age-related reduction in response to short wavelength light. *Exp Gerontol*. 2005;**40**(3):237–242.
55. Najjar RP, *et al*. Aging of non-visual spectral sensitivity to light in humans: compensatory mechanisms? *PLoS One*. 2014;**9**(1):e85837.
56. Benloucif S, *et al*. Responsiveness of the aging circadian clock to light. *Neurobiol Aging*. 2006;**27**(12):1870–1879.
57. Scheuermaier KD, *et al*. Phase shifts to a moderate intensity light exposure in older adults: a preliminary report. *J Biol Rhythms*. 2019;**34**(1):98–104.
58. Cajochen C, *et al*. Evidence that homeostatic sleep regulation depends on ambient lighting conditions during wakefulness. *Clocks and Sleep*. 2019;**1**:517–531.
59. Münch M, *et al*. Effects on subjective and objective alertness and sleep in response to evening light exposure in older subjects. *Behav Brain Res*. 2011;**224**(2):272–278.
60. Pescosolido N, *et al*. Age-related changes in the kinetics of human lenses: prevention of the cataract. *Int J Ophthalmol*. 2016;**9**(10):1506–1517.
61. Kessel L, *et al*. Age-related changes in the transmission properties of the human lens and their relevance to circadian entrainment. *J Cataract Refract Surg*. 2010;**36**(2):308–312.
62. Kessel L, *et al*. Sleep disturbances are related to decreased transmission of blue light to the retina caused by lens yellowing. *Sleep*. 2011;**34**(9):1215–1219.
63. Bitsios P, *et al*. Changes in autonomic function with age: a study of pupillary kinetics in healthy young and old people. *Age Ageing*. 1996;**25**(6):432–438.
64. Sample PA, *et al*. The aging lens: in vivo assessment of light absorption in 84 human eyes. *Invest Ophthalmol Vis Sci*. 1988;**29**(8):1306–1311.
65. Brøndsted AE, *et al*. The effect of cataract surgery on circadian photoentrainment: a randomized trial of blue-blocking versus neutral intraocular lenses. *Ophthalmology*. 2015;**122**(10):2115–2124.
66. Chellappa SL, *et al*. Association of intraocular cataract lens replacement with circadian rhythms, cognitive function, and sleep in older adults. *JAMA Ophthalmol*. 2019;**137**(8):878–885.
67. Chellappa SL, *et al*. Intraocular cataract lens replacement and light exposure potentially impact procedural learning in older adults. *J Sleep Res*. 2020:e13043. doi: 10.1111/jsr.13043.
68. Higuchi S, *et al*. Influence of light at night on melatonin suppression in children. *J Clin Endocrinol Metab*. 2014;**99**(9):3298–3303.
69. Lee SI, *et al*. Melatonin suppression and sleepiness in children exposed to blue-enriched white LED lighting at night. *Physiol Rep*. 2018;**6**(24):e13942.
70. Crowley SJ, *et al*. Increased sensitivity of the circadian system to light in early/mid-puberty. *J Clin Endocrinol Metab*. 2015;**100**(11):4067–4073.
71. Li S, *et al*. The impact of media use on sleep patterns and sleep disorders among school-aged children in China. *Sleep*. 2007;**30**(3):361–367.
72. LeBourgeois MK, *et al*. Digital media and sleep in childhood and adolescence. *Pediatrics*. 2017;**140**(Suppl 2):S92–S96.
73. Egan KJ, *et al*. The role of race and ethnicity in sleep, circadian rhythms and cardiovascular health. *Sleep Med Rev*. 2017;**33**:70–78.
74. Eastman CI, *et al*. Blacks (African Americans) have shorter free-running circadian periods than whites (Caucasian Americans). *Chronobiol Int*. 2012;**29**(8):1072–1077.
75. Eastman CI, *et al*. Circadian rhythm phase shifts and endogenous free-running circadian period differ between African-Americans and European-Americans. *Sci Rep*. 2015;**5**:8381.
76. Paech GM, *et al*. Advancing the sleep/wake schedule impacts the sleep of African-Americans more than European-Americans. *PLoS One*. 2017;**12**(10):e0186887.
77. Malone SK, *et al*. Ethnic differences in sleep duration and morning-evening type in a population sample. *Chronobiol Int*. 2016;**33**(1):10–21.
78. Higuchi S, *et al*. Influence of eye colors of Caucasians and Asians on suppression of melatonin secretion by light. *Am J Physiol Regul Integr Comp Physiol*. 2007;**292**(6):R2352–R2356.
79. Chellappa SL, *et al*. Sex differences in light sensitivity impact on brightness perception, vigilant attention and sleep in humans. *Sci Rep*. 2017;**7**(1):14215.
80. Cowan RL, *et al*. Sex differences in response to red and blue light in human primary visual cortex: a bold fMRI study. *Psychiatry Res*. 2000;**100**(3):129–138.
81. Roenneberg T, *et al*. Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms*. 2003;**18**(1):80–90.
82. Roenneberg T, *et al*. The human circadian clock entrains to sun time. *Curr Biol*. 2007;**17**(2):R44–R45.
83. Martin JS, *et al*. Relationship of chronotype to sleep, light exposure, and work-related fatigue in student workers. *Chronobiol Int*. 2012;**29**(3):295–304.
84. Vollmer C, *et al*. Outdoor light at night (LAN) is correlated with eveningness in adolescents. *Chronobiol Int*. 2012;**29**(4):502–508.
85. Toh KL, *et al*. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science*. 2001;**291**(5506):1040–1043.
86. Ebisawa T. Circadian rhythms in the CNS and peripheral clock disorders: human sleep disorders and clock genes. *J Pharmacol Sci*. 2007;**103**(2):150–154.
87. Takahashi JS, *et al*. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet*. 2008;**9**(10):764–775.
88. Akiyama T, *et al*. An ancestral haplotype of the human PERIOD2 gene associates with reduced sensitivity to light-induced melatonin suppression. *PLoS One*. 2017;**12**(6):e0178373.
89. Chellappa SL, *et al*. Human melatonin and alerting response to blue-enriched light depend on a polymorphism in the clock gene PER3. *J Clin Endocrinol Metab*. 2012;**97**(3):E433–E437.

90. Chellappa SL, *et al*. Light modulation of human sleep depends on a polymorphism in the clock gene Period3. *Behav Brain Res*. 2014;**271**:23–29.
91. Vandewalle G, *et al*. Effects of light on cognitive brain responses depend on circadian phase and sleep homeostasis. *J Biol Rhythms*. 2011;**26**(3):249–259.
92. Lee SI, *et al*. Association between the melanopsin gene polymorphism OPN4*Ile394Thr and sleep/wake timing in Japanese university students. *J Physiol Anthropol*. 2014;**33**:9.
93. Roecklein KA, *et al*. A missense variant (P10L) of the melanopsin (OPN4) gene in seasonal affective disorder. *J Affect Disord*. 2009;**114**(1–3):279–285.
94. Rodgers J, *et al*. Functional characterisation of naturally occurring mutations in human melanopsin. *Cell Mol Life Sci*. 2018;**75**(19):3609–3624.
95. Cajochen C, *et al*. Age-related changes in the circadian and homeostatic regulation of human sleep. *Chronobiol Int*. 2006;**23**(1–2):461–474.
96. Skeldon AC, *et al*. Modelling changes in sleep timing and duration across the lifespan: changes in circadian rhythmicity or sleep homeostasis? *Sleep Med Rev*. 2016;**28**:96–107.
97. Dijk DJ, *et al*. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. *J Physiol*. 1999;**516**(Pt 2):611–627.
98. Santhi N, *et al*. Sex differences in the circadian regulation of sleep and waking cognition in humans. *Proc Natl Acad Sci USA*. 2016;**113**(19):E2730–E2739.
99. Duffy JF, *et al*. Sex difference in the near-24-hour intrinsic period of the human circadian timing system. *Proc Natl Acad Sci USA*. 2011;**108**(Suppl 3):15602–15608.
100. Cain SW, *et al*. Sex differences in phase angle of entrainment and melatonin amplitude in humans. *J Biol Rhythms*. 2010;**25**(4):288–296.
101. Mongrain V, *et al*. Circadian and homeostatic sleep regulation in morningness-eveningness. *J Sleep Res*. 2006;**15**(2):162–166.
102. Schmidt C, *et al*. Homeostatic sleep pressure and responses to sustained attention in the suprachiasmatic area. *Science*. 2009;**324**(5926):516–519.
103. Fischer D, *et al*. Chronotypes in the US—influence of age and sex. *PLoS One*. 2017;**12**(6):e0178782.
104. Chang AM, *et al*. Circadian gene variants influence sleep and the sleep electroencephalogram in humans. *Chronobiol Int*. 2016;**33**(5):561–573.
105. Viola AU, *et al*. PER3 polymorphism predicts sleep structure and waking performance. *Curr Biol*. 2007;**17**(7):613–618.
106. Dashti HS, *et al*. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. *Nat Commun*. 2019;**10**(1):1100.
107. Jones SE, *et al*. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. *Nat Commun*. 2019;**10**(1):343.
108. Haus EL, *et al*. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. *Sleep Med Rev*. 2013;**17**(4):273–284.
109. Lunn RM, *et al*. Health consequences of electric lighting practices in the modern world: a report on the National Toxicology Program's workshop on shift work at night, artificial light at night, and circadian disruption. *Sci Total Environ*. 2017;**607–608**:1073–1084.
110. Bonde JP, *et al*. Work at night and breast cancer–report on evidence-based options for preventive actions. *Scand J Work Environ Health*. 2012;**38**(4):380–390.
111. Ritonja J, *et al*. Working Time Society consensus statements: individual differences in shift work tolerance and recommendations for research and practice. *Ind Health*. 2019;**57**(2):201–212.
112. Rabstein S, *et al*. Differences in twenty-four-hour profiles of blue-light exposure between day and night shifts in female medical staff. *Sci Total Environ*. 2019;**653**:1025–1033.
113. Martin JS, *et al*. Day and night shift schedules are associated with lower sleep quality in Evening-types. *Chronobiol Int*. 2015;**32**(5):627–636.
114. Paksarian D, *et al*. Association of outdoor artificial light at night with mental disorders and sleep patterns among US adolescents. *JAMA Psychiatry*. 2020; e201935. doi: 10.1001/jamapsychiatry.2020.1935.
115. Touitou Y, *et al*. Disruption of adolescents' circadian clock: the vicious circle of media use, exposure to light at night, sleep loss and risk behaviors. *J Physiol Paris*. 2016;**110**(4 Pt B):467–479.
116. Cabré-Riera A, *et al*. Telecommunication devices use, screen time and sleep in adolescents. *Environ Res*. 2019;**171**:341–347.
117. Nagare R, *et al*. Effect of exposure duration and light spectra on nighttime melatonin suppression in adolescents and adults. *Light Res Technol*. 2019;**51**(4):530–543.
118. van der Lely S, *et al*. Blue blocker glasses as a countermeasure for alerting effects of evening light-emitting diode screen exposure in male teenagers. *J Adolesc Health*. 2015;**56**(1):113–119.
119. Howe FE, *et al*. How sensory experiences affect adolescents with an autistic spectrum condition within the classroom. *J Autism Dev Disord*. 2016;**46**(5):1656–1668.
120. Coulter RA. Understanding the visual symptoms of individuals with autism spectrum disorder (ASD). *Optom Vis Dev*. 2009;**40**:164–175.
121. Krakowiak P, *et al*. Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: a population-based study. *J Sleep Res*. 2008;**17**(2):197–206.
122. Wasdell MB, *et al*. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *J Pineal Res*. 2008;**44**(1):57–64.
123. Mazurek MO, *et al*. Bedtime electronic media use and sleep in children with autism spectrum disorder. *J Dev Behav Pediatr*. 2016;**37**(7):525–531.
124. Cho Y, *et al*. Effects of artificial light at night on human health: a literature review of observational and experimental studies applied to exposure assessment. *Chronobiol Int*. 2015;**32**(9):1294–1310.
125. Phillips AJK, *et al*. Irregular sleep/wake patterns are associated with poorer academic performance and delayed circadian and sleep/wake timing. *Sci Rep*. 2017;**7**(1):3216.
126. Stefani O, *et al*. Changing color and intensity of LED lighting across the day impacts on human circadian physiology, sleep, visual comfort and cognitive performance. *BioRxiv*. 2020. doi: 10.1101/2020.04.21.771832.
127. Münch M, *et al*. The role of daylight for humans: gaps in current knowledge. *Clocks & Sleep*. 2020;**2**:61–85.
128. Depner CM, *et al*. Wearable technologies for developing sleep and circadian biomarkers: a summary of workshop discussions. *Sleep*. 2020;**43**(2). doi: 10.1093/sleep/zsz254.