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Review

Understanding light pollution: Recent advances on its health threats and regulations

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ABSTRACT

The prevalence of artificial lights not only improves the lighting conditions for modern society, but also poses kinds of health threats to human health. Although there are regulations and standards concerning light pollution, few of them are based on the potential contribution of improper lighting to diseases. Therefore, a better understanding of the health threats induced by light pollution may promote risk assessment and better regulation of artificial lights, thereby a healthy lighting environment. This review is based on a careful collection of the latest papers from 2018 to 2022 about the health threats of light pollution, both epidemiologically and experimentally. In addition to summing up the novel associations of light pollution with obesity, mental disorders, cancer, etc., we highlight the toxicological mechanism of light pollution via circadian disruption, since light pollution directly interferes with the natural light-dark cycles, and damages the circadian photoentrainment of organisms. And by reviewing the alternations of clock genes and disturbance of melatonin homeostasis induced by artificial lights, we aim to excavate the profound impacts of light pollution based on accumulating studies, thus providing perspectives for future research and guiding relevant regulations and standards.

Introduction

Light pollution is an emerging environmental issue that comes along with intensified urbanization and industrialization. The threats to human health from light pollution have increased dramatically in the past decades (Davies and Smyth, 2018), and it is estimated that today over 80% of the world's population has been impacted by the prevalence of light pollution in different forms (Falchi et al., 2016). According to recent epidemiological research, not only the radiance intensity but also the spectrum and timing of light pollution are the potential factors influencing its association with health outcomes, which promotes artificial light at night (ALAN) and blue light becoming the most popular cases of light pollution (Fonken and Nelson, 2016; Helbich et al., 2020; Maggio et al., 2019; Walker et al., 2020a). Now the potential health impacts of light pollution have been broadened from sleep disorders to many high-concerned diseases like obesity (Abay and Amare, 2018; Esaki et al., 2021), mental disorders (Kim et al., 2018; Namgyal et al., 2020), and cancers (Clarke et al., 2021; Johns et al., 2018; Ritonja et al., 2020). For

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example, some studies discovered the potential association of outdoor/indoor ALAN with breast cancer in Spain and the United States (Garcia-Saenz et al., 2018; Xiao et al., 2020b). The relationship between light pollution and neurodegeneration, with evident early symptoms of Alzheimer's under dim light at night (dLAN), has also been reported (Kim et al., 2018). On the other hand, the discrepancy among studies can never be avoided. The associations mentioned above were questioned in some cases (Johns et al., 2018; Ritonja et al., 2020). Even for those widely-accepted health outcomes, i.e., sleep, the experimental processes were indeed affected by various parameters including time/duration, light wavelength, and the choice of animal model (Batra et al., 2020; Masís-Vargas et al., 2020). Thus, discriminating key factors from those confounders will be essential to identify the actual and direct consequences of light pollution. Considering the toxicological mechanism of light pollution, the circadian rhythm is by far the most significant target which is related to a variety of health outcomes and also under the cooperation of multiple regulatory factors, especially melatonin homeostasis. However, there exists a huge knowledge gap on how light pollution affects detailed processes of circadian photoentrainment, patterning of molecular clocks, and melatonin homeostasis.

This review aims to focus on the research advances in the health impacts of light pollution in the recent five years. After basic introduction of light pollution, we summarized the latest updates in uncovering the links between light pollution and highly concerned health effects (e.g. cancer, obesity, and mental disorders) and relevant toxicological mechanisms. As always, essential roles of disrupted circadian rhythm were highlighted in the causal chain of such health outcomes. Efforts of countries on regulating and controlling light pollution were also discussed. The scope of the light pollution in this review is limited to the ALAN and blue light since other kinds have not been well documented.

1. Light pollution: forms, spectrum and intensities

Although artificial lights have brought many benefits to modern society, the pollution tends to occur when lighting becomes unnecessary, inefficient, and annoying (Chepesiuk, 2009). According to International Dark-Sky Association (2022), light pollution is defined as, "the inappropriate or excessive use of artificial light that can have serious environmental consequences for humans, wildlife, and our climate". The illuminance of a full moon sky under clear conditions is naturally around 0.1-0.3 lux (Gaston et al., 2013), however, even the dim lights in a parking lot and residential side streets could be 10 lux and 5 lux respectively (Gaston et al., 2013). In urban areas, such low levels of lighting at night are ubiquitous, and in some places, the illuminance could even be as high as 150 lux, far brighter than needed (Kyba et al., 2014). Moreover, researchers estimated a spreading rate of 2.2% for light pollution per year, which indicates a rapid expansion of pollution in the near future (Kyba et al., 2017).

Light pollution can occur in a variety of forms. Major components of outdoor light pollution include glare, skyglow, light trespass, and clutter (Table 1). For example, skyglow is widely noticed by astronomers due to its disturbance towards celestial observation. Direct or reflected upward artificial lights scattered in the lower atmosphere, creating a low-intensity (~0.15 lux) diffuse background light in the sky, thus forming skyglow (Gaston et al., 2013). Because of light scattering, the influence scope of skyglow is much larger than areas of lighting sources. Therefore, it is speculated that the negative effects of outdoor light pollution on human health and the ecosystem might be more extensive than expected.

Light pollution is also prevalent indoors, directly increasing the health risks of improper lighting on human health. In addition to light trespassing from the outside, people have a growing number of digital devices emitting different types of light. Devices such as smartphones and laptops emitting blue light are commonly seen at home, as well as lamps and overhead lights emitting white lights. Light-emitting diodes (LEDs) are of particular concern, as the global market share of LEDs for lighting has increased from 5% to over 60% over the last decade and is expected to exceed 80% by 2025 (Gaffuri et al., 2021). At the same time, LEDs provide a narrow light spectrum peaking at blue light (460-500 nm) (Helbich et al., 2020). In contrast, natural light is full-spectrum and dynamic (Fig. 1). The wavelength and intensity of natural light change over time, providing well-timed lighting information to living organisms. Thus, how to maximally mimic the intensity and spectrum of natural light without sacrificing the visual and biological needs of lighting, has become a challenge for designing artificial lights

2. Typical health threats of light pollution

2.1. *Recent evidence in epidemiological studies*

With the advanced satellite-based remote sensing technology, worldwide cohorts can be built up and epidemiological studies provide a great number of causal information for researchers. As a result, novel associations between light pollution and some common health concerns, such as obesity, cancers, and mental disorders, have been suggested, although sleep disorder is still the main negative effect. Table 2 summarized the updated observational research on light pollution in the recent five years (2018-2022).

Human obesity was verified to be positively related to both indoor and outdoor ALAN (Abay and Amare, 2018; Esaki et al., 2021; Park et al., 2019; Zhang et al., 2020), even though the association was stronger in women than in men. As reported by Zhang et al. (2020), the odd ratio (OR) of developing obesity under outdoor ALAN was higher than 1 for both men and women, indicating positive association, while the OR was higher in women (OR = 1.19, 95% confidence interval (CI) = 1.04-1.36) than in men (OR = 1.12, 95% CI = 1.00-1.25). In addition, the positive relationship between night light intensity and women's body weight was nonlinear, since only high stages of light intensities were significantly related to obesity and overweight (Abay and Amare, 2018).

Breast cancer is by far the most studied type of cancer concerning light pollution, but their causal relationship remained somewhat uncertain due to the discrepancy among studies.

Table 1 – Major types of outdoor light pollution.

Type	Detailed description	Typical scenario
Glare	Strong, dazzling light resulting in visual discomfort.	Car headlamps at night.
Skyglow	Illuminated night sky resulted from reflection and scattering of artificial light.	Brightened night sky where the contrast of stars against dark background reduces.
Light trespass	Exterior, spilt light casting where it is unwanted.	Streetlight illuminates an indoor area through the window.
Clutter	Excessive grouping of lighting, generating confusion and distraction.	A cluster of business lights stem from poor placement design.

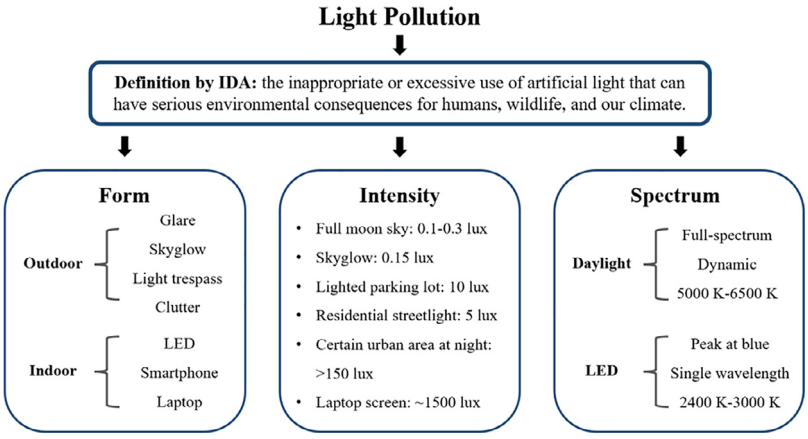

Fig. 1 – Illuminance characteristics of light pollution. IDA: International Dark-Sky Association.

Garcia-Saenz et al. (2018) reported that outdoor ALAN exposure with blue light spectrum had an odd ratio of 1.47 with breast cancer based on cases of over 1,000 Spanish women. Xiao et al. (2021) discovered a significant stage-specific association between overall breast cancer risk and increased ALAN level in different races of women. For Black women, the statistical significance existed only in the localized cancer stage (Hazard Ratio (HR) = 1.45, 95% CI = 0.99-2.14), but it was regional cancer stage in White women (HR = 2.42, 95% CI = 1.07-5.45). The same team also focused on the risk in postmenopausal women participants and found a stronger association for estrogen receptor positive breast cancer than for estrogen receptor negative subtype (Xiao et al., 2020b). However, in some other studies, no relationship was identified between breast cancer and outdoor/indoor ALAN (Clarke et al., 2021; Johns et al., 2018; Ritonja et al., 2020). For instance, Johns et al. (2018) used self-reported ALAN types to examine the night light intensity of participants and found no association, while the light spectrum of ALAN was unknown in their study. Ignoring this characteristic might be the predominant limitation in this study because substantial data have proved that blue light could greatly affect the melatonin system and circadian rhythms (Lockley et al., 2003; Chang et al., 2015). Apart from breast cancer, Garcia-Saenz et al. (2018) reported a strong association between blue outdoor ALAN and prostate cancer in men, with a high odd ratio of 2.05, 95% CI = 1.38-3.03. The team also reported a positive association between blue light ALAN and colorectal cancer, while such a relationship was not observed for longer wavelengths (Garcia-Saenz et al., 2020). In addition, a positive association between ALAN and thyroid cancer incidence was found in a large USA cohort study, and the hazard ratio was stronger in women (HR = 1.91, 95% CI =1.26-2.6) than in men (HR = 1.29, 95% CI = 0.86-1.94) (Zhang et al., 2021).

The association with mental disorders including depression is another recent hotspot for the health issues of ALAN, which has been confirmed by multiple studies in South Korea (Min and Min, 2018b), Japan (Obayashi et al., 2018), and the Netherlands (Helbich et al., 2020). Paksarian et al. (2020) investigated the possible association of outdoor ALAN with various types of mental disorders among US adolescents, and obtained high odd ratios (OR >1) for bipolar disorder (OR = 1.19, 95% CI = 1.05-1.35), specific phobias (OR = 1.18, 95% CI = 1.11-1.26), and major depressive disorder or dysthymia (OR = 1.07, 95% CI = 1.00-1.15) (Paksarian et al., 2020). In one cross-sectional research, indoor ALAN was significantly related to manic symptoms in bipolar disorder patients (OR = 2.15, 95% CI = 1.09-4.22) (Esaki et al., 2020).

There are also longitudinal studies investigating the association between bedroom ALAN and incident diabetes (Obayashi et al., 2020) and carotid atherosclerosis (Obayashi et al., 2019) based on the Japanese HEIJO-KYO cohort. The results showed that ALAN was causally related to both diseases, and the strong relationship remained for diabetes even when the indoor ALAN decreased to 3 lux. Sorensen et al. (2020) investigated the contribution of outdoor light intensity to the risk factors of cardiovascular disease and found that body mass index (BMI), systolic blood pressure (SBP), and low-density lipoprotein (LDL) but not FPG (fasting plasma glucose) were positively associated with in-

Table 2 – Observational studies discussing relationships between light pollution and common health problems (2018-2022).

Health problem	Research year	Setting	Population demographics	Assessment of lighting condition	Main results and conclusions	Reference
Obesity	2008 and 2013.	Nigeria.	18,667 women (2008) and 14,919 women (2013).	Satellite-based outdoor ALAN intensity.	Nonlinear relationship was reported for night light intensity and body weight.	Abay and Amare, 2018
	2003-2009 and follow-up at 2015.	USA and Puerto Rico.	43,722 women.	Self-reported indoor ALAN in different types.	All ALAN exposure types were positively associated with obesity (BMI ≥30), and sleeping with a television or light was closely linked to gaining 5 kg or more (RR = 1.17, 95% CI = 1.08-1.27).	Park et al., 2019
	1995-1996 and follow-up (2004-2006).	USA.	A sample of 239,781 men and women (aged 50-71) who were not obese at baseline (1995-1996).	Outdoor ALAN in unit of radiance ($nW/(cm^2 \cdot sr)$ from satellite data.	Higher outdoor ALAN at baseline was associated with higher developing obesity possibility (BMI ≥30) over 10 years (men (OR = 1.12, 95% CI = 1.00-1.25), women (OR = 1.19, 95% CI = 1.04-1.36).	Zhang et al., 2020
	2017 and 2019.	Japan.	200 people with bipolar disorder.	Bedroom ALAN measured at 1-min intervals at the head and eye level (ALAN ≥ 3 lux).	Group under ALAN were reported with higher obesity (BMI ≥ 25, OR = 2.13, 95% CI = 1.19-4.21) than the control, together with higher body weight (68.7 vs. 64.4 kg; $p = 0.03$).	Esaki et al., 2021
Cancer	2003-2012 (average 6.1 years of follow-up).	UK.	105,866 women with no previous history of breast cancer at the baseline.	Self-reported ALAN types.	No association was discovered between ALAN level and breast cancer risk, and a reduced premenopausal breast cancer risk was reported with a history of night waking around age 20.	Johns et al., 2018
	2008-2013.	Spain.	1219 breast cancer cases, 1385 female controls, 623 prostate cancer cases, and 879 male controls.	Indoor ALAN through the questionnaire and outdoor ALAN using images of Madrid and Barcelona taken by astronauts aboard the ISS in 2012.	Exposure to outdoor ALAN in the blue light spectrum was associated with breast cancer (OR = 1.47, 95% CI = 1.00-2.17) and prostate cancer (OR = 2.05, 95% CI = 1.38-3.03). And for indoor ALAN, men had a higher risk of prostate cancer (OR = 2.79, 95% CI = 1.55-5.04), whereas women had a lower risk of breast cancer (OR = 0.77; 95% CI = 0.39-1.51).	Garcia-Saenz et al., 2018
	2007-2013.	Spain.	661 histologically verified colorectal cancer cases and 1322 controls.	Outdoor ALAN levels based on satellite data.	Positive association was reported between exposure to blue light and colorectal cancer (OR = 1.6; 95% CI = 1.2-2.2), while no such association was found for light of full spectrum (OR = 1.0; 95% CI = 0.7-1.2).	Garcia-Saenz et al., 2020
	2005-2010.	Canada.	844 breast cancer cases and 905 controls.	Outdoor ALAN based on two satellite data sources.	No association between residential outdoor ALAN and breast cancer for either measure of ALAN.	Ritonja et al., 2020
	1995-1996 and follow-up (2004-2005).	USA.	186,981 postmenopausal women including 12,318 incident postmenopausal breast cancer cases.	Outdoor ALAN estimated from satellite imagery at baseline (1996).	Positive association between postmenopausal breast cancer and outdoor ALAN (HR = 1.10, 95% CI = 1.02-1.18), and stronger association for ER^+ breast cancer (HR = 1.12, 95% CI = 1.02-1.24) than for ER^- cancer (HR = 1.07, 95% CI = 0.85-1.34).	Xiao et al., 2020b

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Table 2 (*continued*)

Health problem	Research year	Setting	Population demographics	Assessment of lighting condition	Main results and conclusions	Reference
	2004 and 2017.	USA.	30,518 black and 12,982 white women.	Outdoor ALAN estimated from satellite image at baseline (2004).	A significant association between high breast cancer risk overall and increased ALAN level was reported (HR = 1.27, 95% CI = 1.00-1.60), and in Black woman it was observed for breast cancer in localized stage only, but regional stage in White woman.	Xiao et al., 2021
	1995-1996 and follow-up (2004-2006).	USA.	464,371 participants (183,103 women and 281,268 men).	Outdoor ALAN measured by satellite in unit of nW/(cm^2·sr).	A positive association was found between ALAN and thyroid cancer (HR = 1.55, 95% CI = 1.18-2.02). The association was stronger in women (HR = 1.81, 95% CI = 1.26-2.60) than men (HR = 1.29, 95% CI = 0.86-1.94.	Zhang et al. 2021
	1993 or 1999 (baseline) through 2012.	Denmark.	16,941 nurses from the Danish Nurse Cohort.	Outside ALAN estimated from U.S. DMSP in year 1996, 1999, 2000, 2003, 2004, 2006, and 2010.	No association was found between ALAN and overall breast cancer, but a suggestive association was reported between ER$^-$ breast cancer and ALAN.	Clarke et al., 2021
Mental Disorder	2009.	South Korea.	2009 Korean Community Health Survey (113,119 assessed for depression and 152,159 for suicide).	Outdoor ALAN map from ArcMap 10.4 (ESRI, Redlands, CA, USA) in 2009.	People living under the highest levels of outdoor ALAN had more depressive symptoms (OR = 1.29, 95% CI = 1.15-1.46) or suicidal behaviors (OR = 1.27, 95% CI = 1.16-1.39).	Min and Min, 2018b
	2010-2014 and follow-up (2014-2015).	Japan.	863 participants who did not have depressive symptoms at baseline.	Bedroom ALAN measured at 1-min interval for two consecutive nights (ALAN average ≥5 lux).	The group under indoor ALAN showed a significant higher depression risk (HR = 1.89, 95% CI = 1.13-3.14), and the significance remained when adjusted.	Obayashi et al., 2018
	2001-2004.	USA.	10,123 adolescents aged 13 to 18 years.	Outdoor ALAN measured by satellite in unit of nW/(cm^2·sr).	Outdoor ALAN was positively associated with past-year mood and anxiety disorder, bipolar disorder, specific phobias and major depressive disorder (OR all >1).	Paksarian et al., 2020

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Table 2 (*continued*)

Health problem	Research year	Setting	Population demographics	Assessment of lighting condition	Main results and conclusions	Reference
	2017 and 2019.	Japan.	370 patients with bipolar diseases (BD).	Bedroom ALAN measured for 7 nights (ALAN average ≥3 lux).	Bedroom light exposure at night is significantly associated with manic symptoms in BD patients (OR = 2.15, 95% CI = 1.09-4.22).	Esaki et al., 2020
	2018.	Netherlands.	10,482 participants aged 18-65.	Outdoor ALAN data from satellite in unit of nW/(cm^2·sr).	People in the highest ALAN quintile showed significantly higher PHQ-9 score (indicative of depressive symptoms) than the lowest (β = 0.541, 95% CI = 0.141-0.941) when adjusted for confounders.	Helbich et al., 2020
Carotid Atherosclerosis	2010-2014 and follow-up (2016-2017).	Japan.	945 participants at baseline and 780 at follow-up.	Bedroom ALAN measured for 2 consecutive nights.	High indoor ALAN intensity was significantly associated with a significant increase in mean carotid intima-media thickness when adjusted for confounders (β = 0.028, 95% CI = 0.005-0.052, p = 0.019).	Obayashi et al., 2019
Diabetes	2010-2014 and follow-up (2016-2017).	Japan.	678 community-dwelling elderly without diabetes at baseline.	Bedroom ALAN measured at 1-min interval for two nights (ALAN average ≥ 5 lux).	Diabetic incidence rate was significantly higher in the ALAN group than the dark group (incidence rate ratio = 3.74; 95% CI = 1.55-9.05), and the significance remained when the exposure decreased to 3 lux.	Obayashi et al., 2020
Sleep problem	1995-1996.	USA.	137,360 women and 196,005 men.	Outdoor ALAN data in 1996 using ArcGIS.	The highest quintile of outdoor ALAN was associated with 16% and 25% increases in the likelihood of short sleeps in women (MOR = 1.16, 95% CI = 1.10-1.22) and men (MOR = 1.25, 95% CI = 1.19-1.31).	Xiao et al., 2020a
	2002-2013.	South Korea.	52,027 adults aged 60 or more.	Outdoor ALAN satellite data based on visible light intensity.	Increased outdoor ALAN was related to rising hypnotic prescriptions and daily dose intake (β = 17.07, p < 0.0001 for all hypnotic drugs).	Min and Min, 2018a
Cardiovascular disease (CVD)	2003-2005 and 2010-2012.	India.	6944 participants.	Outdoor ALAN intensity collected by satellite.	CVD risk factors BMI, SBP and LDL but not FPG were positively associated with increasing outdoor ALAN.	Sorensen et al., 2020

ALAN: artificial light at night; OR: odd ratio; RR: risk ratio; HR: hazard ratio; CI: confidence interval; BMI: body mass index; SBP: systolic blood pressure; LDL: low-density lipoprotein; FPG: fasting plasma glucose; MOR: multinomial odds ratio.

creasing outdoor ALAN. Meanwhile, two studies analyzed the association with sleep problems, justifying the predominant contribution of increasing outdoor ALAN to shorter sleep duration and rising hypnotic prescriptions separately (Min and Min, 2018a; Xiao et al., 2020a).

2.2. *Laboratory-based studies*

2.2.1. *Cancer*

According to the technical report of cancer hazard assessment conducted by the National Institute of Environmental Health Sciences (2021), ALAN can function as an environmental oncogenic factor promoting the proliferation and progression of tumors. Previous studies identified key carcinogen characteristics such as increased oxidative stress, altered immune system, and dysregulated cell proliferation under ALAN (Navara and Nelson, 2007). In the recent five years, relevant research progressed to investigate major signaling pathways and epigenetic modifications involved in the ALAN-induced carcinogenicity, as well as the wavelength-dependent effects. Xiang et al. (2019) demonstrated rapid tumor growth and activated intrinsic resistance to paclitaxel in rats with MCF-7 breast tumor xenografts after exposure to dLAN. Through disruption of the circadian melatonin system by dLAN, the IL-6/STAT3/DNMT1 signaling pathway was activated, thereby inhibiting the tumor suppressor ARH1. Zubidat et al. (2018) investigated how ALAN of different wavelengths impacts the tumor growth in breast-cancer-cell-inoculated female BALB/c mice. The results showed ALAN of short wavelength induced increased tumor growth, increased global DNA methylation, and promoted lung metastases formation, while the effects of long wavelength were relatively lessened. This team also observed lower but tissue-specific enzymatic activity of DNA methyltransferases under ALAN (Agbaria et al., 2019). However, the causal link between blue light and cancer is still controversial. Daytime blue light exposure helps maintain a healthy circadian rhythm and enhances the motility of the photoreceptive T lymphocytes, thereby promoting immune functions (Merrill and Frutos, 2020; Phan et al., 2016). Thus, whether time matters in the carcinogenicity of blue light expects further explorations.

2.2.2. *Metabolic disorders*

The association between metabolic disorders and light pollution has not attracted much attention till recently. Both chronic and acute exposure to light pollution can affect the metabolism of many endogenous molecules such as glucocorticoids and lipids (Fleury et al., 2020; Nelson and Chbeir, 2018). Under long-term ALAN exposure for 8 weeks, the increased body weight and exacerbated metabolic abnormalities were found in the mice model of type 2 diabetes mellitus, but the disruption of insulin resistance was reversed upon return to dark nights (Russart et al., 2019). Another study aimed whether the impacts of light pollution were associated with color temperature (Alaasam et al., 2018). It was found that three-week LED night light treatment with the higher color temperature at 5000 K (compared with 3000 K) in the zebra finch (*Taeniopygia guttata*) caused a large increase in corticosterone level from pretreatment, as well as increased nighttime activity, and no sex-dependent difference was observed.

For the short-term ALAN exposure, adipose tissue of zebra finch exhibited the obvious pro-inflammatory state, indicating the susceptibility of immune and endocrine patterns to ALAN (Mishra et al., 2019). Masís-Vargas et al. (2020) compared the metabolic profiling of male Wistar rats under different colors of short-term ALAN exposure and at varied time points during the dark phase. The energy expenditure and metabolism-related gene expression in the liver were acutely disturbed under ALAN even in low intensities. Moreover, all the observed effects are dependent on the time of day and the wavelength of light, suggesting potential involvement of circadian system and light perception respectively. The team also provided further evidence for the deleterious effects of blue light at night on glucose metabolism based on diurnal Sudanian grass rats (*Arvicanthis ansorgei*) (Masís-Vargas et al., 2019). Interestingly, there was an acute sex-dependent impact of blue light on glucose metabolism in this study. Increased sugar intake and reduced insulin secretion were significant especially in males, together with higher glucose intolerance. In addition, although widely confirmed by animal studies, analogous impacts on glucose homeostasis were not found in humans (Chamorro et al., 2021). After two nights of indoor ALAN exposure (<5 lux), disturbed sleep architecture and quality were discovered without changing the metabolism of glucose, insulin, and c-peptide. Thus, it remained to be investigated whether alternation of glucose metabolism is specific to blue light, or is widely witnessed under artificial light.

2.2.3. *Mental and neurological disorders*

Recent research suggested that even acute exposure to ALAN has the potential to cause neurological changes and phenotypes of mental disorders. When exposing mice to 5 lux of ALAN for 3 consecutive nights, depression-like behavior could occur, together with the changed contents of proinflammatory cytokines and neurotrophins in the hippocampus (Walker et al., 2020b). Moreover, a potential compensatory mechanism was reported in exposed male mice, as expressions of clock gene *clock* and *cry1* significantly increased at ZT2 compared to male controls. However, other studies demonstrated no or reversible depression-like phenotypes under chronic ALAN exposure (Bedrosian et al., 2013b; Castro et al., 2005), suggesting the research needs to further investigate the potential compensatory mechanism for mental disorders under ALAN exposure.

Under the treatment of artificial light, the alternations associated with neurodegeneration, a highly-concerned health issue, are extensively evident. The abnormity in the dopaminergic system is regarded as one kind of the prominent biomarkers for Parkinson's disease. Romeo et al. (2013) reported the increased formation of neuromelanin and reduced dopamine (DA) neurons in the *substantia nigra* after being exposed to bright light (fluorescent lamp) continuously for 20 or 90 days. Aumann et al. (2016) examined tyrosine hydroxylase and DA transporter immunoreactivity in human postmortem brain tissue in summer and winter. It was found that in summer the density of tyrosine hydroxylase-positive neurons was significantly (~6-fold) higher than that in winter, but it was unclear whether such difference was induced by varied photoperiods or because of greater usage of indoor ar-

tificial light in winter. By exposing tauopathy flies to dLAN (10 lux) for 3 days, the increased formation of phosphorylated Tau was observed in those Alzheimer's Disease flies, as well as disrupted rhythmic behaviors and altered sleep-wake cycles, together indicating circadian disruption and a promotion of neurodegeneration (Kim et al., 2018). Similarly, Namgyal et al. (2020) evaluated the effects of dLAN (5 lux) on Swiss Albino mice for three weeks. The impairment of cognitive and non-cognitive behavior, and the downregulations of BDNF, CREB, SIRT1 mRNAs and neurodegeneration-associated miRNA21a-5p and miRNA34a-5p were reported. Apart from dLAN, exposure to blue light in the daylight also induced retinal damage, brain neurodegeneration, and impaired locomotion of fruit flies. The increased areas of vacuoles indicated neuronal death in the brain, eventually leading to premature aging of flies (Nash et al., 2019).

2.2.4. *Sleep disorders*

Sleep disorder is the representative of rhythmic health concerns induced by light pollution, and mounting previous evidence has already demonstrated the detrimental effects of inappropriate light conditions on sleep/wake behavior and sleep duration (Aulsebrook et al., 2018). Recent laboratory research further investigated the influences on detailed sleep architecture and sleep parameters. The study conducted by Panagiotou et al. (2020) demonstrated that even in a short duration of one-day dLAN exposure, sleep was already influenced, and the situations became worse with prolonged dLAN exposure. By examining the network of sleep deterioration, it was discovered that the Electroencephalography (EEG) power density spectra values were attenuated in mice exposed to three months of dLAN. Meanwhile, it was suggested that chronic (three months) dLAN exposure led to more significant changes in the young's sleep architecture towards a previously established aging phenotype, while for the elderly the age-associated sleep alternations were enhanced (Panagiotou and Deboer, 2020). There is also a study demonstrating no statistical differences in sleep parameters such as slow-wave sleep (SWS), or rapid eye movement (REM) sleep for dLAN exposed mice (Borniger et al., 2013). A likely explanation of the disparity in results is that potential compensatory mechanisms might render the organism partly adjustable and able to cope (Mentink et al., 2020). The nature of such a compensation strategy is proposed as the homeostatic regulation of sleep. Homeostatic and circadian processes together determine most aspects of sleep performance (Deboer, 2018). However, the compensation is not a panacea. Once exceeding a certain threshold, the compensatory mechanisms could not remain in operation anymore. This phenomenon is evident under the three-month prolonged dLAN exposure (Panagiotou and Deboer, 2020).

However, it is worth noting that most of the existed studies are based on the nocturnal models (mouse or rat), which needs to be very careful to extrapolate their experimental findings to human health since nocturnal and diurnal species have distinct light-responding sleep patterns. An increasing number of researchers begin to choose various diurnal species, such as diurnal birds or vertebrates for further investigations in recent years. For example, Batra et al. (2020) exposed diurnal female zebra finches to 5 lux dLAN for three weeks, and sleep loss and fragmented sleep at night were observed. The results also showed altered hypothalamic expression pattern of genes involved in the circadian timing and sleep regulation, suggesting dLAN's effects on Ca^{2+}-dependent sleep-inducing pathway.

3. Toxicological mechanisms: circadian disruption

The circadian rhythm of living organisms consists of internal biological clocks that synchronized with external environmental cues such as light to maintain proper timekeeping (Masri and Sassone-Corsi, 2018). A healthy circadian system provides rhythmic regulation to the vast majority of physiological and behavioral processes, such as sleep/wake behaviors, daily metabolism, cardiovascular function, cognition, and memory (Patke et al., 2020; Reinke and Asher, 2019). While under excessive environmental light pressure, such as ALAN which greatly disrupts the natural light cycles, the circadian system can be challenged and physiological disorders and diseases would occur as mentioned above (Chepesiuk, 2009; McNamara et al., 2011).

3.1. *Circadian photoentrainment*

Since light acts as the predominant "zeitgeber" for circadian rhythms of living organisms, light pollution can directly interfere with the natural photoentrainment of circadian clocks. The evolutionarily conserved circadian rhythm mainly consists of three parts: the input pathway, the central clock, and the output pathway. For mammals, the retina at the back of the eyes employs various photoreceptors to receive light information. Then retinal ganglion cells (RGCs), the output neurons of the retina, signal to the central clock suprachiasmatic nucleus (SCN) in the brain (Wassle, 2004). Peripheral oscillators further receive timing cues from the central pacemaker SCN via humoral and/or neural signals and then regulate local physiology, psychology, and behavior.

In-depth investigations reported that a small subset of RGCs expressing the photopigment melanopsin is specified for light detection of the circadian system (Hattar et al., 2002; Hattar et al., 2003). They are called intrinsically photosensitive RGCs (ipRGCs). Throughout the light spectrum, ipRGCs are most vulnerable to blue light, in which condition circadian photoentrainment also presents peak sensitivities (Hatori and Panda, 2010). This potentially implies the health risks of blue-emitting LEDs toward ipRGCs (Hatori et al., 2017). ipRGCs have extensive projections to over a dozen of brain regions, including those with profound implications for circadian rhythms (SCN), mood (peri-habenula), sleep and wake (hypothalamus, the ventrolateral preoptic area) (Mure, 2021; Schmidt et al., 2011). Especially, the innervation from ipRGCs to its major target SCN is essential to orchestrate biological clocks and drive circadian coherence. Genetic ablation of ipRGCs in mice almost completely impaired the circadian photoentrainment in SCN, while vision formation was not influenced (Guler et al., 2008).

The central pacemaker SCN has around 10,000-20,000 neurons regulating animal circadian behaviors. Within the SCN,

there are mainly two subregions, the "core" and the "shell", characterized by different neurochemical properties (Liu et al., 2007; Swaab et al., 1985; Videnovic et al., 2014). The retinorecipient core contains neurons secreting vasoactive intestinal polypeptide (VIP) and gastrin-releasing peptide (GRP), while those secreting arginine vasopressin (AVP) and prokineticin 2 (PK2) are mostly located in the shell (Colwell, 2011; Golombek and Rosenstein, 2010). VIP neurons in SCN are indispensable in generating circadian locomotion in mammals (Todd et al., 2020). They are also essential for the normal resetting of daily rhythms responding to environmental light cues by spontaneous calcium signaling (Jones et al., 2018). When blocking the activity of these neurons, the light-induced phase shifts in locomotion was compromised. In addition to synchronizing with the environment, neurons in SCN also need to keep pace with each other. They communicate through synaptic transmission and form interconnected circuits. After photoentrainment from ipRGCs, neurotransmitters such as γ-aminobutyric acid (GABA) and VIP are released from presynaptic core neurons and bind to their receptors in the postsynaptic shell neurons, and result in the subsequent events like phosphorylation of CREB (cAMP-response element-binding protein) and induction of PER and CRY transcription, thereby establishing a new circadian phase (Liu et al., 2007; Welsh et al., 2010). This also implies the tight coupling of SCN neurons, making SCN more robust facing environmental challenges.

Peripheral clocks are involved in many tissues such as liver, lung, kidney, heart, and adipose tissue, and abundant evidence has demonstrated the essential role of circadian timing in their normal physiological functions. For example, liver and pancreatic clocks control the homeostasis of glucose, and the circadian clock in muscles rather than in the brain is essential for the normal activity and bodyweight of mice (Patke et al., 2020). These organs receive signals directly from SCN, or SCN-mediated messages primarily via neuroendocrine pathways, thus achieving the overall synchronization to changing environment. Meanwhile, the rhythms of hormones are widely considered markers of endogenous rhythmicity. For instance, SCN directly controls the secretion of melatonin in the pineal, then this light-responsive hormone circulates from the brain to all areas of the body, regulating sleep/wake cycles and rhythmic activities (Gunata et al., 2020).

3.2. *Patterning of molecular clocks*

Approximately 10% of the whole mammalian genome is controlled by the clock genes, thus a well-organized molecular network of clock genes is essential (Masri and Sassone-Corsi, 2018). The molecular circadian clock in mammals is comprised of two transcriptional-translational feedback loops, with a set of clock genes oscillating around 24 hr period. In the core loop, positive elements CLOCK and BMAL1 form heterodimeric complexes and bind to E-box sequences in the enhancer/promoter regions of PER and CRY (Patke et al., 2020). Then PER and CRY increased their expression in daytime together with clock-controlled genes. At night, such accumulation of PER and CRY in turn inhibits the transcription of CLOCK-BMAL1, thereby impeding their own expression and inducing a restart of the circadian rhythm. The other ancillary loop mainly concerns two nuclear receptors, REV-ERB and RORα. They either repress or activate the transcription of the BMAL1 via REV response elements (RREs) (Preitner et al., 2002; Sato et al., 2004). The secondary loop functions to stabilize and enhance the whole clock oscillating process (Nawrot et al., 2018).

Light can directly evoke alternations of molecular clock genes, and the outcomes vary with the time point of exposure. Nighttime light exposure induces a phase shift of molecular clocks, while daytime light treatment causes no significant changes (Colwell, 2011). The epigenetic modifications of molecular clocks are suggested as one prominent action mechanism. They mainly include histone modifications and DNA methylation, where heritable alternations of gene expression happen without changing the DNA sequence (Sahar and Sassone-Corsi, 2013). For example, Ser10 in histone H3's tail in SCN clock cells was phosphorylated under nighttime light pulse (Crosio et al., 2000). The expressions of *c-fos* and PER1 were induced as well. In addition, genome-wide methylation analysis showed altered epigenetic patterns of more than 5000 CpG sites in long-term shift workers, especially low levels of CLOCK promoter methylation and high levels of CRY2 promoter methylation (Stevens and Zhu, 2015), yet whether ALAN could trigger similar methylation alternations is largely unknown.

At the molecular level, nighttime dim light exposure can alter the expression of clock genes in both SCN and peripheral tissues. It is estimated that the typical light level in the sleeping environment is around 5 lux, which is five times brighter than the natural level (i.e., under moonlight) (Gaston et al., 2012). When mice were exposed under a light (~150 lux)/dim light (5 lux) cycle for a month, the hypothalamus molecular clocks were affected both in gene and protein levels, with the decreased rhythm amplitude in PER1 and PER2 expressions (Fonken et al., 2013). And BMAL1 expression in the SCN showed an attenuated oscillation in Wistar rats in a 12 hr light (150-200 lux):12 hr dim white light (5 lux dLAN) schedule (Stenvers et al., 2016). Similar attenuation effects of rhythm amplitude under dLAN are reported in insects and hamsters (Bedrosian et al., 2013a; Honnen et al., 2019). The detrimental effects on the master clock SCN can further influence peripheral clocks, even though the SCN can adjust more rapidly than rhythms in peripheral tissues when responding to advanced or delayed environmental lighting cycle (Yamazaki et al., 2000). For instance, dLAN suppresses the amplitude of REV-ERB mRNA expression in the liver as well (Fonken et al., 2013).

Altered expression of clock genes is also considered one prominent pathogenic factor of many diseases associated with light pollution, thus it might help explain the health threats of light pollution. Take neurodegeneration as an example, a significant positive association of BMAL1 and PER1 genes with Parkinson's Disease was discovered in Chinese patients (Gu et al., 2015). Videnovic et al. (2016) examined relationships between expressions of PER1,2,3, and BMAL1 in whole blood of PD patients with disease severity, sleep quality, and daytime sleepiness of PD. The results showed that the phase of the four clock genes was distinct in patients with different levels of daytime somnolence and sleep quality. Two neurodegeneration-associated microRNAs, miRNA21a-5p and

miRNA34a-5p, were also found to be downregulated by the three-week exposure to 5 lux indoor ALAN (Namgyal et al., 2020).

3.3. *Melatonin homeostasis*

The melatonin system has always been considered the major physiological target of ALAN, especially blue light. Recent studies advanced on monitoring its role in diseases that are newly associated with light pollution. Melatonin is required for many circadian processes, and melatonin secretion itself obeys a certain rhythm (Xie et al., 2017). To be more specific, in humans and diurnal animals, melatonin is produced at night to increase sleep propensity and its maximum plasma level peaks at 3-4 a.m. (Lavie, 1997; Zisapel, 2018). The irregular level and circadian timing of melatonin will further disrupt its physiological and neurological functions. For example, melatonin possesses an anti-amyloidogenic effect and prevents the β-amyloid fibril production in the brain, which plays significant protection against Alzheimer's disease (Gunata et al., 2020; Shukla et al., 2017). Furthermore, by supplementing melatonin in the PD animal model, the levels of antioxidant enzymes were improved and excess oxidative stress was suppressed (Saravanan et al., 2007). Thus, the melatonin level is considered a biomarker for the progression of neurodegeneration. Melatonin could also affect the hypothalamus-pituitary-ovary axis and further reduce the production of estrogen, thereby low melatonin levels and high estrogen levels are well characterized during the development of breast cancer (Jaynes and Switzer, 2021). It could also improve cell adhesion and impede the invasion potential of breast cancer cells in *in vitro* tests (El-Sokkary et al., 2019).

Numerous studies have manifested that melatonin suppression is highly sensitive to light of short wavelength. For instance, healthy human beings under 6.5 hr nighttime exposure to 460 nm monochromatic light (blue) showed a two-fold greater circadian phase than under 555 nm light (green) and a dramatic melatonin suppression ranging from 65% to 96% (Lockley et al., 2003). The blue-enriched electric light from eReader before bedtime led to a 55.12% $\pm$ 20.12% reduction in evening plasma melatonin levels for participants, and a delay of over 1.5 hr of melatonin onset was also reported (Chang et al., 2015). Moreover, it was found that both flickering blue light and non-flickering blue light could acutely suppress salivary melatonin, and the decrease of melatonin under flickering blue light was significantly lower than the other (Kozaki et al., 2020).

4. Implications for the regulation of light pollution

Public concerns have been raised due to the increased knowledge about various health outcomes of light pollution, and laws and regulations for controlling the potential implications of light pollution have been issued in some countries. Early in 2002, the Czech Republic acted as the first nation to outlaw excess outdoor light (Clarke, 2002), and all outdoor light fixtures are required to be shielded to prevent light from going above the horizontal. In the United Kingdom, the Clean Neighbourhoods and Environment Act was updated in 2005 to incorporate nuisance from artificial light (Taylor, 2006). The French Decree on the prevention, reduction, and limitation of light pollution gives detailed technical requirements for the design and operation of outdoor lighting installations (Barentine, 2019). Especially, the Decree restricts the emission of blue light by requiring that the correlated color temperature (CCT) of light should be less than 3,000 K in all instances. The allowable illumination levels are also clarified to prevent excessive lighting.

Apart from national legislation, standards and regional ordinances at different levels also play important roles in restricting light pollution. For example, China has paid growing attention to the regulation of light pollution since two decades ago. The national standard "General Specifications for Build Environment (GB 55016-2021)" implemented from April 1st 2022 requires impact analysis of reflected light from glass screen wall in areas surrounding residential buildings, hospitals, schools, etc. In Shanghai, light pollution prevention measures enacted successively from 2011 to 2013 cover aspects of residential, commercial, and exterior building lighting. Limitations including maximum light intensity, vertical illuminance, and upward light output ratio of luminaires are hierarchically regulated based on the division of environmental zones (Shanghai Municipal Bureau of Quality and Technical Supervision, 2012).

However, the adverse health impacts currently make up a small proportion in the consideration of light pollution regulation. Saving energy and reduction in background interference during all-purpose observation are still the major goals of restricting environmental lighting (Guanglei et al., 2019). For example, the Seoul metropolitan government of South Korea enacted an ordinance on light pollution prevention and management in July 2010. According to the ordinance, the purpose was to "improve the quality of life for citizens, protect ecosystems, and save energy by preventing unnecessary lighting practices", and "light environment management zones" are classified more on different demands of production and life, rather than potential health risks of environmental lighting. In Light Pollution Prevention Measures of Shanghai, psychological interference of light at a subjective level and/or eye fatigue are the only health-related evaluations when establishing relevant standards. Therefore, providing abundant evidence and suggestions on lighting thresholds based on health concerns is also one of the major tasks for light pollution management in a more scientific way.

5. Conclusions and perspectives

This review has focused on research advances about the health threats of light pollution in the recent five years (2018-2022). Researchers broadened the effects of ALAN and blue light to more profound diseases like neurodegeneration and cancer, and vital contributing factors are identified in the causal relationships. Epidemiologically, recent studies progressed to more accurately adjusting confounding factors, and verified the significance of light wavelength, intensity, and timing, even though the discordancy among studies still ex-

isted. Animal studies distinguished the effects of acute and chronic exposure, and relevant toxicological investigations have been centered around circadian disruption. It was discovered that chronic exposure to light pollution tends to cause overall circadian disturbance and acute experiments mainly cause effects on peripheral tissues. The sex-, wavelength-, and time-dependent alternations under light pollution were also newly documented, but they were not always evident due to different experimental settings and the choice of the animal model. Of note, we highlighted the disruption of the melatonin system as a crucial risk factor linking the epidemiology of light pollution, particularly under blue light, and the toxicological pathway from circadian photoreceptor ipRGCs to the melatonin system has attracted growing attention. At last, we summarized the history and current status of light pollution regulations worldwide and reported the deficiency of considering extensive health threats in formulating relevant policies and regulations. In the future, more efforts about light pollution should shed light on the missing information on the following issues:

(1) The association between light pollution and breast cancer has been verified by epidemiological and animal studies, while concerns about other kinds of cancers are quite insufficient. In addition, the potential roles of sex difference in those non-reproductive cancers resulting from light pollution need further investigations.
(2) Circadian disruption is a major health outcome observed in both acute and chronic exposures to light pollution. Of note, most existing animal studies are based on murine models, while careful consideration should be given as the biological rhythm of these nocturnal animals is largely different from humans. The application of diurnal animal models is thus expected to provide a necessary supplement for relevant studies.
(3) Combined pollution is quite common in the real environment, and light is commonly co-existed with airborne particulate matters and chemicals. These pollution factors highly overlap during the afternoon and evening in urban cities. Till now, only new studies documented the short-term combined effects of ALAN with $PM_{2.5}$. Their potential synergetic health threats remain to be revealed.
(4) Developing countries such as China caught up in the last two decades by establishing regional ordinances and standards, while the integrated regulation especially at the national level still lacks. More efforts should be made to improve relevant laws, including the establishment of lighting limits based on profound health outcomes other than only eye fatigue.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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REFERENCES

Abay, K.A., Amare, M., 2018. Night light intensity and women's body weight: evidence from Nigeria. Econ. Hum. Biol. 31, 238–248.
Agbaria, S., Haim, A., Fares, F., Zubidat, A.E., 2019. Epigenetic modification in 4t1 mouse breast cancer model by artificial light at night and melatonin the role of DNA-methyltransferase. Chronobiol. Int. 36, 629–643.
Alaasam, V.J., Duncan, R., Casagrande, S., Davies, S., Sidher, A., Seymoure, B., et al., 2018. Light at night disrupts nocturnal rest and elevates glucocorticoids at cool color temperatures. J. Exp. Zool. Part A 329, 465–472.
Aulsebrook, A.E., Jones, T.M., Mulder, R.A., Lesku, J.A., 2018. Impacts of artificial light at night on sleep: a review and prospectus. J. Exp. Zool. Part A 329, 409–418.
Aumann, T.D., Raabus, M., Tomas, D., Prijanto, A., Churilov, L., Spitzer, N.C., et al., 2016. Differences in number of midbrain dopamine neurons associated with summer and winter photoperiods in humans. PLoS One 11, e0158847.
Barentine, J., 2019. France adopts national light pollution policy among most progressive in the world. Avaliable: https://www.darksky.org/france-light-pollution-law-2018/#:~:text=A%20new%20law%20came%20into,of%20light%20in%20outdoor%20spaces. Assessed January 20, 2022.
Batra, T., Malik, I., Prabhat, A., Bhardwaj, S.K., Kumar, V., 2020. Sleep in unnatural times: Illuminated night negatively affects sleep and associated hypothalamic gene expressions in diurnal zebra finches. Proc. R. Soc. B: Biol. Sci. 287, 20192952.
Bedrosian, T.A., Galan, A., Vaughn, C.A., Weil, Z.M., Nelson, R.J., 2013a. Light at night alters daily patterns of cortisol and clock proteins in female siberian hamsters. J. Neuroimmunol. 25, 590–596.
Bedrosian, T.A., Weil, Z.M., Nelson, R.J., 2013b. Chronic dim light at night provokes reversible depression-like phenotype: Possible role for tnf. Mol. Psychiatr. 18, 930–936.
Borniger, J.C., Weil, Z.M., Zhang, N., Nelson, R.J., 2013. Dim light at night does not disrupt timing or quality of sleep in mice. Chronobiol. Int. 30, 1016–1023.
Castro, J.P., Frussa-Filho, R., Fukushiro, D.F., Chinen, C.C., Abílio, V.C., Silva, R.H., 2005. Effects of long-term continuous exposure to light on memory and anxiety in mice. Physiol. Behav. 86, 218–223.
Chamorro, R., Wilms, B., Holst, A., Röhl, C., Mölle, M., Knaak, A., et al., 2021. Acute mild dim light at night slightly modifies sleep but does not affect glucose homeostasis in healthy men. Sleep. Med. 84, 158–164.
Chang, A.M., Aeschbach, D., Duffy, J.F., Czeisler, C.A., 2015. Evening use of light-emitting ereaders negatively affects sleep, circadian timing, and next-morning alertness. Proc. Natl. Acad. Sci. USA 112, 1232–1237.
Chepesiuk, R., 2009. Missing the dark health effects of light pollution. Environ. Health. Persp. 117, A20–A27.
Clarke, R.B., Amini, H., James, P., von Euler-Chelpin, M., Jørgensen, J.T., Mehta, A., et al., 2021. Outdoor light at night and breast cancer incidence in the Danish nurse cohort. Environ. Res. 194, 110631.
Clarke, T., 2002. Day one for light pollution law. Available: https://www.nature.com/articles/news020527-14#:~:text=From%201%20June%2C%20all%20outdoor,

especially%20over%20cities%2C%20less%20dark. Assessed January 22, 2022.
Colwell, C.S., 2011. Linking neural activity and molecular oscillations in the scn. Nat. Rev. Neurosci. 12, 553–569.
Crosio, C., Cermakian, N., Allis, C.D., Sassone-Corsi, P., 2000. Light induces chromatin modification in cells of the mammalian circadian clock. Nat. Neurosci. 3, 1241–1247.
Davies, T.W., Smyth, T., 2018. Why artificial light at night should be a focus for global change research in the 21st century. Glob. Chang. Biol. 24, 872–882.
Deboer, T., 2018. Sleep homeostasis and the circadian clock: Do the circadian pacemaker and the sleep homeostat influence each other's functioning? Neurobio. Sleep. Circadian Rhythm. 5, 68–77.
El-Sokkary, G.H., Ismail, I.A., Saber, S.H., 2019. Melatonin inhibits breast cancer cell invasion through modulating DJ-1/KLF17/ID-1 signaling pathway. J. Cell. Physiol. 120, 3945–3957.
Esaki, Y., Obayashi, K., Saeki, K., Fujita, K., Iwata, N., Kitajima, T., 2020. Association between light exposure at night and manic symptoms in bipolar disorder: cross-sectional analysis of the apple cohort. Chronobiol. Int. 37, 887–896.
Esaki, Y., Obayashi, K., Saeki, K., Fujita, K., Iwata, N., Kitajima, T., 2021. Bedroom light exposure at night and obesity in individuals with bipolar disorder: a cross-sectional analysis of the apple cohort. Physiol. Behav. 230, 113281.
Falchi, F., Cinzano, P., Duriscoe, D., Kyba, C.C.M., Elvidge, C.D., Baugh, K., et al., 2016. The new world atlas of artificial night sky brightness. Sci. Adv. 2 (6), e1600377.
Fleury, G., Masís-Vargas, A., Kalsbeek, A., 2020. Metabolic implications of exposure to light at night: lessons from animal and human studies. Obesity 28, S18–S28.
Fonken, L.K., Aubrecht, T.G., Meléndez-Fernández, O.H., Weil, Z.M., Nelson, R.J., 2013. Dim light at night disrupts molecular circadian rhythms and increases body weight. J. Biol. Rhythm. 28, 262–271.
Fonken, L.K., Nelson, R.J., 2016. Effects of light exposure at night during development. Curr. Opin. Behav. Sci. 7, 33–39.
Gaffuri, P., Stolyarova, E., Llerena, D., Appert, E., Consonni, M., Robin, S., et al., 2021. Potential substitutes for critical materials in white LEDs: technological challenges and market opportunities. Renew. Sust. Energ. Rev. 143, 110869.
Garcia-Saenz, A., de Miguel, A.S., Espinosa, A., Costas, L., Aragonés, N., Tonne, C., et al., 2020. Association between outdoor light-at-night exposure and colorectal cancer in spain. Epidemiology 31, 718–727.
Garcia-Saenz, A., Sánchez de Miguel, A., Espinosa, A., Valentin, A., Aragonés, N., Llorca, J., et al., 2018. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (mcc-Spain study). Environ. Health. Persp. 126, 047011.
Gaston, K.J., Bennie, J., Davies, T.W., Hopkins, J., 2013. The ecological impacts of nighttime light pollution: a mechanistic appraisal. Biol. Rev. 88, 912–927.
Gaston, K.J., Davies, T.W., Bennie, J., Hopkins, J., 2012. Reducing the ecological consequences of night-time light pollution: options and developments. J. Appl. Ecol. 49, 1256–1266.
Golombek, D.A., Rosenstein, R.E., 2010. Physiology of circadian entrainment. Physiol. Rev. 90, 1063–1102.
Gu, Z., Wang, B., Zhang, Y.B., Ding, H., Zhang, Y., Yu, J., et al., 2015. Association of arntl and per1 genes with Parkinson's disease: a case-control study of han Chinese. Sci. Rep. 5, 15891.
Guanglei, W., Ngarambe, J., Kim, G., 2019. A comparative study on current outdoor lighting policies in china and korea: a step toward a sustainable nighttime environment. Sustainability 11, 3989.
Guler, A.D., Ecker, J.L., Lall, G.S., Haq, S., Altimus, C.M., Liao, H.W., et al., 2008. Melanopsin cells are the principal conduits for rod-cone input to non-image-forming vision. Nature 453, 102–105.
Gunata, M., Parlakpinar, H., Acet, H.A., 2020. Melatonin: A review of its potential functions and effects on neurological diseases. Rev. Neurol. 176, 148–165.
Hatori, M., Gronfier, C., Van Gelder, R.N., Bernstein, P.S., Carreras, J., Panda, S., et al., 2017. Global rise of potential health hazards caused by blue light-induced circadian disruption in modern aging societies. NPJ. Aging. Mech. Dis. 3, 9.
Hatori, M., Panda, S., 2010. The emerging roles of melanopsin in behavioral adaptation to light. Trends. Mol. Med. 16, 435–446.
Hattar, S., Liao, H.W., Takao, M., Berson, D.M., Yau, K.W., 2002. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science 295 (5557), 1065–1070.
Hattar, S., Lucas, R.J., Mrosovsky, N., Thompson, S., Douglas, R.H., Hankins, M.W., et al., 2003. Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. Nature 424, 76–81.
Helbich, M., Browning, M., Huss, A., 2020. Outdoor light at night, air pollution and depressive symptoms: a cross-sectional study in the netherlands. Sci. Total. Environ. 744, 140914.
Honnen, A.C., Kypke, J.L., Hölker, F., Monaghan, M.T., 2019. Artificial light at night influences clock-gene expression, activity, and fecundity in the mosquito culex pipiens. Molestus. Sustain. 11, 6220.
International Dark-Sky Association, 2022. Light pollution. Available: https://www.darksky.org/light-pollution. Assessed January 15, 2022.
Jaynes, D., Switzer, P., 2021. Nighttime blue light exposure and breast cancer. Osteopath. Fam. Physician 13, 30–33.
Johns, L.E., Jones, M.E., Schoemaker, M.J., McFadden, E., Ashworth, A., Swerdlow, A.J., 2018. Domestic light at night and breast cancer risk: A prospective analysis of 105 000 UK women in the generations study. Brit. J. Cancer 118, 600–606.
Jones, J.R., Simon, T., Lones, L., Herzog, E.D., 2018. Scn vip neurons are essential for normal light-mediated resetting of the circadian system. J. Neurosci. 38, 7986–7995.
Kim, M., Subramanian, M., Cho, Y.H., Kim, G.H., Lee, E., Park, J.J., 2018. Short-term exposure to dim light at night disrupts rhythmic behaviors and causes neurodegeneration in fly models of Tauopathy and Alzheimer's disease. Bioche. Bioph. Res. Co. 495, 1722–1729.
Kozaki, T., Hidaka, Y., Takakura, J.Y., Kusano, Y., 2020. Salivary melatonin suppression under 100-hz flickering blue light and non-flickering blue light conditions. Neurosci. Lett. 722, 134857.
Kyba, C.C.M., Hanel, A., Holker, F., 2014. Redefining efficiency for outdoor lighting. Energ. Environ. Sci. 7, 1806–1809.
Kyba, C.C.M., Kuester, T., Sánchez de Miguel, A., Baugh, K., Jechow, A., Hölker, F., et al., 2017. Artificially lit surface of earth at night increasing in radiance and extent. Sci. Adv. 3, e1701528.
Lavie, P., 1997. Melatonin: role in gating nocturnal rise in sleep propensity. J. Biol. Rhythms. 12, 657–665.
Liu, A.C., Lewis, W.G., Kay, S.A., 2007. Mammalian circadian signaling networks and therapeutic targets. Nat. Chem. Biol. 3, 630–639.
Lockley, S.W., Brainard, G.C., Czeisler, C.A., 2003. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J. Clin. Endocrinol. Metab. 88, 4502–4505.
Maggio, R., Vaglini, F., Rossi, M., Fasciani, I., Pietrantoni, I., Marampon, F., et al., 2019. Parkinson's disease and light: the bright and the dark sides. Brain. Res. Bull. 150, 290–296.
Masís-Vargas, A., Hicks, D., Kalsbeek, A., Mendoza, J., 2019. Blue light at night acutely impairs glucose tolerance and increases

sugar intake in the diurnal rodent arvicanthis ansorgei in a sex-dependent manner. Physiol. Rep. 7, e14257.
Masís-Vargas, A., Ritsema, W.I.G.R., Mendoza, J., Kalsbeek, A., 2020. Metabolic effects of light at night are time- and wavelength-dependent in rats. Obesity 28, S114–S125.
Masri, S., Sassone-Corsi, P., 2018. The emerging link between cancer, metabolism, and circadian rhythms. Nat. Med. 24, 1795–1803.
McNamara, J.M., Barta, Z., Klaassen, M., Bauer, S., 2011. Cues and the optimal timing of activities under environmental changes. Ecol. lett. 14, 1183–1190.
Mentink, L.J., Thomas, J., Melis, R.J.F., Olde Rikkert, M.G.M., Overeem, S., Claassen, J., 2020. Home-eeg assessment of possible compensatory mechanisms for sleep disruption in highly irregular shift workers - the anchor study. PLoS One 15, e0237622.
Merrill, R.M., Frutos, A.M., 2020. Ecological evidence for lower risk of lymphoma with greater exposure to sunlight and higher altitude. High Alt. Med. Biol. 21, 37–44.
Min, J.Y., Min, K.B., 2018a. Outdoor artificial nighttime light and use of hypnotic medications in older adults: a population-based cohort study. J. Clin. Sleep. Med. 14, 1903–1910.
Min, J.Y., Min, K.B., 2018b. Outdoor light at night and the prevalence of depressive symptoms and suicidal behaviors: A cross-sectional study in a nationally representative sample of Korean adults. J. Affect. Disorders. 227, 199–205.
Mishra, I., Knerr, R.M., Stewart, A.A., Payette, W.I., Richter, M.M., Ashley, N.T., 2019. Light at night disrupts diel patterns of cytokine gene expression and endocrine profiles in zebra finch (*Taeniopygia guttata*). Sci. Rep. 9, 15833.
Mure, L.S., 2021. Intrinsically photosensitive retinal ganglion cells of the human retina. Front. Neurol. 12, 636330.
Namgyal, D., Chandan, K., Sultan, A., Aftab, M., Ali, S., Mehta, R., et al., 2020. Dim light at night induced neurodegeneration and ameliorative effect of curcumin. Cells 9, 2093.
Nash, T.R., Chow, E.S., Law, A.D., Fu, S.D., Fuszara, E., Bilska, A., et al., 2019. Daily blue-light exposure shortens lifespan and causes brain neurodegeneration in drosophila. Npj. Aging. Mech. Dis. 5, 8.
National Institute of Environmental Health Sciences, 2021. NTP cancer hazard assessment report on night shift work and light at night Available from doi:10.22427/NTP-CHR-NSWLAN.
Navara, K.J., Nelson, R.J., 2007. The dark side of light at night: physiological, epidemiological, and ecological consequences. J. Pineal Res. 43 (3), 215–224.
Nawrot, T.S., Saenen, N.D., Schenk, J., Janssen, B.G., Motta, V., Tarantini, L., et al., 2018. Placental circadian pathway methylation and in utero exposure to fine particle air pollution. Environ. Int. 114, 231–241.
Nelson, R.J., Chbeir, S., 2018. Dark matters: effects of light at night on metabolism. P. Nutr. Soc. 77, 223–229.
Obayashi, K., Saeki, K., Kurumatani, N., 2018. Bedroom light exposure at night and the incidence of depressive symptoms: a longitudinal study of the heijo-kyo cohort. Am. J. Epidemiol. 187, 427–434.
Obayashi, K., Yamagami, Y., Kurumatani, N., Saeki, K., 2020. Bedroom lighting environment and incident diabetes mellitus: a longitudinal study of the heijo-kyo cohort. Sleep. Med. 65, 1–3.
Obayashi, K., Yamagami, Y., Tatsumi, S., Kurumatani, N., Saeki, K., 2019. Indoor light pollution and progression of carotid atherosclerosis: a longitudinal study of the heijo-kyo cohort. Environ. Int. 133, 105184.
Paksarian, D., Rudolph, K.E., Stapp, E.K., Dunster, G.P., He, J., Mennitt, D., et al., 2020. Association of outdoor artificial light at night with mental disorders and sleep patterns among us adolescents. JAMA. Psychiat. 77, 1266–1275.
Panagiotou, M., Deboer, T., 2020. Effects of chronic dim-light-at-night exposure on sleep in young and aged mice. Neurosci 426, 154–167.
Panagiotou, M., Rohling, J.H.T., Deboer, T., 2020. Sleep network deterioration as a function of dim-light-at-night exposure duration in a mouse model. Clocks. Sleep. 2, 308–324.
Park, Y.M.M., White, A.J., Jackson, C.L., Weinberg, C.R., Sandler, D.P., 2019. Association of exposure to artificial light at night while sleeping with risk of obesity in women. JAMA. Intern. Med. 179, 1061–1071.
Patke, A., Young, M.W., Axelrod, S., 2020. Molecular mechanisms and physiological importance of circadian rhythms. Nat. Rev. Mol. Cell. Biol. 21, 67–84.
Preitner , N., Damiola , F., Lopez-Molina , L., Zakany , J., Duboule , D., Albrecht , U., et al., 2002. The orp han nuc lea r receptor REV-ERBalpha controls circadian transcription within the positive limb of the mammalian circadian oscillator. Cell 110, 251–260.
Reinke, H., Asher, G., 2019. Crosstalk between metabolism and circadian clocks. Nat. Rev. Mol. Cell. Biol. 20, 227–241.
Ritonja, J., McIsaac, M.A., Sanders, E., Kyba, C.C.M., Grundy, A., Cordina-Duverger, E., et al., 2020. Outdoor light at night at residences and breast cancer risk in canada. Eur. J. Epidemiol. 35, 579–589.
Romeo , S., Viaggi , C., Di Camillo , D., Willis , A.W., Lozzi , L., Rocchi , C., et al., 2013. Bright li g ht e xpos ure reduces TH-positive dopamine neurons: Implications of light pollution in Parkinson's disease epidemiology. Sci. Rep. 3, 1395.
Russart, K.L.G., Chbeir, S.A., Nelson, R.J., Magalang, U.J., 2019. Light at night exacerbates metabolic dysfunction in a polygenic mouse model of type 2 diabetes mellitus. Life Sciences 231, 116574.
Sahar, S., Sassone-Corsi, P., 2013. The epigenetic language of circadian clocks. Handb. Exp. Pharmacol. 29–44.
Saravanan, K.S., Sindhu, K.M., Mohanakumar, K.P., 2007. Melatonin protects against rotenone-induced oxidative stress in a hemiparkinsonian rat model. J. Pineal. Res. 42, 247–253.
Sato, T.K., Panda, S., Miraglia, L.J., Reyes, T.M., Rudic, R.D., McNamara, P., et al., 2004. A functional genomics strategy reveals rora as a component of the mammalian circadian clock. Neuron 43, 527–537.
Schmidt, T.M., Chen, S.K., Hattar, S., 2011. Intrinsically photosensitive retinal ganglion cells: Many subtypes, diverse functions. Trends Neurosci. 34, 572–580.
Shanghai Municipal Bureau of Quality and Technical Supervision, 2012. Specifications on urban environment (decoration) lighting. Available: http://std.samr.gov.cn/db/search/stdDBDetailed?id=91D99E4D2E422E24E05397BE0A0A3A10. Assessed January 10, 2022.
Shukla, M., Govitrapong, P., Boontem, P., Reiter, R.J., Satayavivad, J., 2017. Mechanisms of melatonin in alleviating alzheimer's disease. Curr. Neuropharmacol. 15, 1010–1031.
Sorensen, T.B., Wilson, R., Gregson, J., Shankar, B., Dangour, A.D., Kinra, S., 2020. Is night-time light intensity associated with cardiovascular disease risk factors among adults in early-stage urbanisation in south india? A cross-sectional study of the andhra pradesh children and parents study. BMJ. Open 10, e036213.
Stenvers, D.J., van Dorp, R., Foppen, E., Mendoza, J., Opperhuizen, A.L., Fliers, E., et al., 2016. Dim light at night disturbs the daily sleep-wake cycle in the rat. Sci. Rep. 6, 35662.
Stevens, R.G., Zhu, Y., 2015. Electric light, particularly at night, disrupts human circadian rhythmicity: Is that a problem? Philoso. T. R. Soc. B. 370, 20140120.
Swaab, D.F., Fliers, E., Partiman, T.S., 1985. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain. Res. 342, 37–44.

Taylor, M.M., 2006. Light pollution and nuisance: the enforcement guidance for light as a statutory nuisance. JPL 8, 1114–1127.
Todd, W.D., Venner, A., Anaclet, C., Broadhurst, R.Y., De Luca, R., Bandaru, S.S., et al., 2020. Suprachiasmatic vip neurons are required for normal circadian rhythmicity and comprised of molecularly distinct subpopulations. Nat. Commun. 11 (1), 1–20.
Videnovic, A., Lazar, A.S., Barker, R.A., Overeem, S., 2014. The clocks that time us'-circadian rhythms in neurodegenerative disorders. Nat. Rev. Neurol. 10, 683–693.
Videnovic, A., Marconi, A., Zee, P., Klerman, E., Turek, F., 2016. Circadian expression of clock genes in Parkinson's disease - implications for disrupted sleep and daytime sleepiness (s19.008). Neurol 86 S19.008.
Walker, W.H., Bumgarner, J.R., Walton, J.C., Liu, J.A., Melendez-Fernandez, O.H., Nelson, R.J., et al., 2020a. Light pollution and cancer. Int. J. Mol. Sci. 21 (24), 9360.
Walker, W.H., Borniger, J.C., Gaudier-Diaz, M.M., Hecmarie Meléndez-Fernández, O., Pascoe, J.L., Courtney, De.Vries, et al., 2020b. Acute exposure to low-level light at night is sufficient to induce neurological changes and depressive-like behavior. Mol. Psychiatr. 25, 1080–1093.
Wassle, H., 2004. Parallel processing in the mammalian retina. Nat. Rev. Neurosci. 5, 747–757.
Welsh, D.K., Takahashi, J.S., Kay, S.A., 2010. Suprachiasmatic nucleus: cell autonomy and network properties. Annu. Rev. Physiol. 72, 551–577.
Xiang, S., Dauchy, R.T., Hoffman, A.E., Pointer, D., Frasch, T., Blask, D.E., et al., 2019. Epigenetic inhibition of the tumor suppressor arhi by light at night-induced circadian melatonin disruption mediates stat3-driven paclitaxel resistance in breast cancer. J. Pineal Res. 67, e12586.
Xiao, Q., Gee, G., Jones, R.R., Jia, P., James, P., Hale, L., 2020a. Cross-sectional association between outdoor artificial light at night and sleep duration in middle-to-older aged adults: The NIH-AARP diet and health study. Environ. Res. 180, 108823.
Xiao, Q., Gierach, G.L., Bauer, C., Blot, W.J., James, P., Jones, R.R., 2021. The association between outdoor artificial light at night and breast cancer risk in black and white women in the southern community cohort study. Environ. Health Perspect. 129, 87701.
Xiao, Q., James, P., Breheny, P., Jia, P., Park, Y., Zhang, D., et al., 2020b. Outdoor light at night and postmenopausal breast cancer risk in the nih-aarp diet and health study. Int. J. Cancer 147, 2363–2372.
Xie, Z., Chen, F., Li, W.A., Geng, X., Li, C., Meng, X., et al., 2017. A review of sleep disorders and melatonin. Neurol. Res. 39, 559–565.
Yamazaki, S., Numano, R., Abe, M., Hida, A., Takahashi, R.I., Ueda, M., et al., 2000. Resetting central and peripheral circadian oscillators in transgenic rats. Science 288, 682–685.
Zhang, D., Jones, R.R., Powell-Wiley, T.M., Jia, P., James, P., Xiao, Q., 2020. A large prospective investigation of outdoor light at night and obesity in the NIH-AARP diet and health study. Environ. Health 19.
Zhang, D., Jones, R.R., James, P., Kitahara, C.M., Xiao, Q., 2021. Associations between artificial light at night and risk for thyroid cancer: a large US cohort study. Cancer 127 (9), 1448–1458.
Zisapel, N., 2018. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. Br. J. Pharmacol. 175 (16), 3190–3199.
Zubidat, A.E., Fares, B., Fares, F., Haim, A., 2018. Artificial light at night of different spectral compositions differentially affects tumor growth in mice: interaction with melatonin and epigenetic pathways. Cancer Control 25, 1073274818812908.