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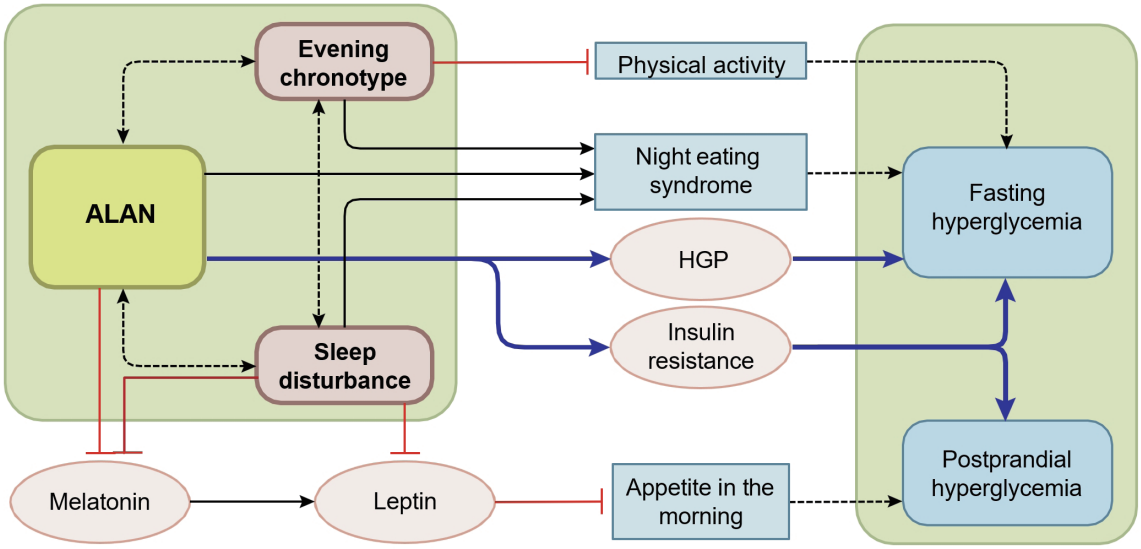

Highlights

- **ALAN is a pervasive environmental exposure disrupting circadian rhythms.**
- **Indoor or outdoor ALAN exposure links to a higher risk of developing T2DM.**
- **ALAN characteristics, beyond intensity, can impair glucose metabolism.**
- **ALAN, sleep health, and lifestyle factors have a complex interplay.**
- **Managing ALAN, with chronotherapy and chrononutrition, may improve diabetes care.**

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Artificial Light at Night and Type 2 Diabetes Mellitus

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The widespread and pervasive use of artificial light at night (ALAN) in our modern 24-hour society has emerged as a substantial disruptor of natural circadian rhythms, potentially leading to a rise in unhealthy lifestyle-related behaviors (e.g., poor sleep; shift work). This phenomenon has been associated with an increased risk of type 2 diabetes mellitus (T2DM), which is a pressing global public health concern. However, to date, reviews summarizing associations between ALAN and T2DM have primarily focused on the limited characteristics of exposure (e.g., intensity) to ALAN. This literature review extends beyond prior reviews by consolidating recent studies from 2000 to 2024 regarding associations between both indoor and outdoor ALAN exposure and the incidence or prevalence of T2DM. We also described potential biological mechanisms through which ALAN modulates glucose metabolism. Furthermore, we outlined knowledge gaps and investigated how various ALAN characteristics beyond only light intensity (including light type, timing, duration, wavelength, and individual sensitivity) influence T2DM risk. Recognizing the detrimental impact of ALAN on sleep health and the behavioral correlates of physical activity and dietary patterns, we additionally summarized studies investigating the potential mediating role of each component in the relationship between ALAN and glucose metabolism. Lastly, we proposed implications of chronotherapies and chrononutrition for diabetes management in the context of ALAN exposure.

Keywords: Circadian rhythm; Diabetes mellitus, type 2; Dietary patterns; Exercise; Insulin resistance; Light pollution; Sleep

INTRODUCTION

In a modern 24-hour society, where people in cities (e.g., New York City) never sleep, and technology such as smartphones permeates every aspect of our lives, the social boundary between day and night has become indistinct [1]. In addition, more people tend to go to bed late, wake up early, and thereby experience shorter sleep durations. This trend has increased over time [2,3] and is particularly noticeable among Asians compared to non-Hispanic White adults, according to a global ecological study [2]. Among the United States (US) population, the prevalence of sleep deprivation was higher among Blacks compared to White individuals, and the disparities were widest in individuals with middle or high-income status, women, and young and middle-aged adults [3]. One consequence of this social shift is the pervasive exposure to artificial light at night (ALAN), which refers to any anthropogenic illumination at night, both indoors and outdoors [4]. This can include lights from commercial buildings and homes, streetlights, billboards, and other forms of outdoor lighting [4]. Individuals are more prone to exposure to ALAN in situations such as night shift work, using electric devices before bedtime, and experiencing social jet lag [5]. An estimated 15% to 20% of all workers were engaged in night or rotating shift work in

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most industrialized countries [6], and 39% of Americans used cell phones in their bedrooms during the hour before sleep [7].

Exposure to ALAN can cause substantial circadian rhythm disruption [8,9] and altered metabolism [10] that compromise human health through conditions such as obesity [11,12], cancers [13-15], and cardiovascular diseases [16]. However, the literature addressing the association between ALAN and type 2 diabetes mellitus (T2DM) remains relatively sparse compared to studies examining the relationship with other health problems. In addition, previous studies have been limited to investigating only the exposure to or intensity of ALAN. Also, studies investigating the potential impact of ALAN exposure on T2DM risk were accessed by evaluating environmental factors that increase exposure to ALAN (e.g., night shift work, night-time lifestyle). For example, circadian misalignment by shift work increased the risk of T2DM by about 10% to 40% [17], with cumulative excess risk of up to 60% of T2DM with increasing duration of shift work [18]. In addition, night shift work was independently associated with poorer glycemic control in patients with T2DM [19]. Evening chronotypes were more likely to have unhealthy lifestyle behaviors and independently higher incident [20] and prevalent [21] T2DM risk than morning chronotypes.

To comprehend the association between ALAN exposure and the risk or prevalence of T2DM, we conducted a literature review of recently published observational and experimental studies (from January 2000 to June 2024). This review categorized ALAN exposure into indoor and outdoor settings, facilitating a thorough and organized examination of their association with glucose metabolism. In addition, we reviewed mechanisms elucidating the impact of ALAN on glucose metabolism and highlighted additional factors to consider when defining ALAN exposure beyond light intensity. Subsequently, we summarized literature investigating the potential mediating role of circadian alternations by sleep and the behavioral correlates of physical activity and dietary patterns on the association between ALAN exposure and abnormal glucose metabolism. Furthermore, we assessed existing literature to understand the impact of ALAN on the management and pharmacological treatment (e.g., chronotherapy) strategies for patients with T2DM. Lastly, we underscore the need for further research to address knowledge gaps considering the role of pervasive ALAN exposure in preventing and managing T2DM.

TYPE OF ALAN AND EPIDEMIOLOGIC EVIDENCE

Outdoor ALAN

Nearly a quarter of the global land area already lies under artificially light-polluted night-time skies, and ALAN affects at least 80% of the world's population [20]. Pervasive exposure to ALAN encompasses a wide range of lighting, including streetlights, commercial and residential lighting, and lights from industrial facilities. Satellite images of the earth at night illustrate the extent of the distribution of artificial light sources that have been used as a measure of light pollution [21]. Various techniques and methods have been used to measure outdoor ALAN in research, including illuminators, satellite data, interactive online maps, or self-reported questionnaires [22]. Among them, satellite data from the US Department of Defense's Defense Meteorological Satellite Program (DMSP) were generally used to define the outdoor ALAN level at ground level in ecological studies [23]. Satellite-detectable light has increased globally by 49% over 25 years (from 1992 to 2017) [24], and ALAN exposure in urban cities is increasing rapidly at a rate of 5% to 20% per year [25]. Overall, satellite-based measurements of upward radiance (measured in watts per steradian per square meter) were well correlated with ground-based measurements of illumination (measured in lux) [26]. However, the radiance measurements derived from satellite data failing to accurately account for the changes in luminous efficacy resulting from the transition to light-emitting diode (LED) lighting is a challenge that future research must address [27]. A drawback of DMSP data, which had frequent and unrecorded changes in sensor gain, was improved by providing higher radiometric sensitivity with globally calibrated night-time radiance measurements by the Visible Infrared Imaging Radiometer Suite Day-Night Band (VIIRS DNB) [28].

Epidemiologic evidence

There were two cross-sectional studies and one prospective cohort study to evaluate the association between outdoor ALAN using DMSP and T2DM risk (Table 1). The levels of outdoor ALAN in the studies reviewed here were measured using DMSP data, either as categorical variables [29,30] or log-scaled continuous variables [31]. A cross-sectional study based on a Chinese nationwide survey showed that high intensity of outdoor satellite-assessed ALAN (highest vs. lowest quintile) was associated with higher odds of prevalent T2DM (odds ratio [OR],

Table 1. Studies on the relationship between artificial light at night and diabetes risk

Study	Setting	Population demographics	Type of ALAN exposure	Assessment of diabetes outcomes	Main results and conclusions	Confounding factors
Outdoor ALAN						
Zheng et al. (2023) [29]	Cross-sectional study	Adult (aged ≥18; mean age, 42.7) *n*=98,658 (men: 50.9%)	Method: DMSP Intensity: quintiles (Q1–5) and continuous variable Exposure: year 2010 Time: NA Wavelength: NA	FPG ≥126 mg/dL or 2hPG ≥200 mg/dL or HbA1c ≥6.5% or previously diagnosed diabetes	The highest quintile of LAN was associated with increased prevalence of diabetes compared to the lowest quintile (PR, 1.28; 95% CI, 1.03–1.60)	Age, sex, education, smoking, drinking, physical activity, family history of diabetes, household income, residential area, taking antihypertensive or lipid-lowering medications, and BMI
Xu et al. (2023) [30]	Prospective cohort study (UK Biobank)	Adults (aged 37–73; mean age, 55.9) *n*=283,374 (men: 48.2%)	Method: DMSP Intensity: quartiles (Q1–4) Exposure: average value of annual outdoor LAN during follow-up Time: NA Wavelength: NA	ICD-10 codes (E11) by hospital inpatients records	The highest quantile was related to increased diabetes risk compared to the lowest quantile (HR, 1.14; 95% CI, 1.02–1.27) The exposure-response curve of incident T2DM increases monotonically, with a plateau at the highest level (*P* for non-linear=0.014)	Age, sex, ethnicity, education level, economic activity, household income, smoking, alcohol frequency, physical activity level, sedentary time, shift work, health diet score, population density, housing score, income score, air pollution level, noise at night, and PRS score
Sorensen et al. (2020) [31]	Cross-sectional study	Adults (aged >18; median age, 40 for women and 29 for men) *n*=5,328 (men: 54%)	Method: NTLI by satellite data from DMSP Intensity: log-scaled, continuous variable Exposure: NA Time: NA Wavelength: NA	FPG (continuous)	There was no association between NTLI and FPG (β=−0.002; 95% CI, −0.1 to 0.1)	Age, sex, caste (India), religion, marital status, and survey season
Indoor ALAN						
Obayashi et al. (2014) [36]	Cross-sectional study	Elderly individuals (aged ≥60; mean age, 72.7) *n*=513 (men: 46.4%)	Method: ambulatory light meter Intensity: average light intensity (continuous variable) Exposure: 2 consecutive days Time: evening (4-hr before bedtime) Wavelength: NA	Diabetes (based on medical history, current diabetes treatment, or FPG ≥126 mg/dL, or HbA1c ≥6.5%)	Prevalent diabetes (OR, 1.72; 95% CI, 1.12–2.64) The evening light exposure increased from 17.5 (25%) to 37.6 lux (75%), associated with a 51.2% increase in prevalent diabetes.	Sex, BMI, sleep duration
Obayashi et al. (2020) [37]	Prospective cohort study (median, 42 months FU)	Elderly individuals (≥60 years old) *n*=678	Method: portable light meter Intensity: LAN (average ≥5 lux) vs. dark (average <5 lux; reference) Exposure: 2 consecutive bedtime nights Time: from bedtime and rise time Wavelength: NA	Diabetes (based on medical history, current diabetes medications, or HbA1c ≥6.5%)	The incident rate for diabetes was higher in the LAN group than in the dark group (IRR, 3.19; 95% CI, 1.38–7.47; *P*=0.007)	Age, sex, smoking, drinking, education, household income, BMI, hypertension, caloric intake, bedtime and rise time, daytime physical activity, and daytime light exposure
Xu et al. (2022) [38]	Cohort study (1 year FU)	Young adults (aged 16–22; mean age, 18.8) *n*=484 (men: 38.7%)	Method: portable illuminance meter Intensity: (1) 1-hr and 4-hr average intensity of post-bedtime light; (2) average light intensity from bedtime to rising time; (3) 1-hr and 2-hr average intensity of pre-awake light (continuous variable) Exposure: 7 consecutive days Time: night (between bedtime and awake) Wavelength: NA	HOMA-IR, CM risk score (continuous var.; calculated from the score sum of waist circumference, blood pressure, lipid profile, HOMA-IR)	Higher average ALAN exposure (all night) was associated with an increase in CM risk score (β=1.47; 95% CI, 0.69–2.25) Exposure time: post-bedtime light exposure (within 1 to 4 hr) was associated with increased HOMA-IR	Age, sex, BMI, smoking, drinking status, socioeconomic status, physical activity, food addiction, sleep duration, sugar-sweetened beverages consumption, screen time

(*Continued to the next page*)

Table 1. Continued

Study	Setting	Population demographics	Type of ALAN exposure	Assessment of diabetes outcomes	Main results and conclusions	Confounding factors
Windred et al. (2024) [39]	Prospective cohort study (2006–2010)	Mild aged individuals (aged 40–69) *n*=84,790 (men: 42%)	Method: light sensor Intensity: 4 percentile ranges Exposure: 7 consecutive days Time: day and night (0:30 AM–6:00 AM) Wavelength: NA	Diabetes (based on hospital admission records, death register)	Dose-dependent relationship between brighter LAN and higher risk of T2DM (90–100th percentiles, HR, 1.53; 95% CI, 1.32–1.77)	Age, sex, ethnicity, income, material deprivation, education, employment status, smoking/alcohol, healthy diet, physical activity, and urbanicity
Kim et al. (2023) [40]	Cross-sectional study (2007–2010)	Elderly individuals (aged 65–84) *n*=552	Method: actigraphy Intensity: average 0 > light value during 5-hr nadir (L5, log-scaled) light value during the 5-hr nadir (LAN) vs. 5-hr period of complete darkness per 24-hr (reference; no-LAN) Exposure: 7 consecutive days Time: during sleep Wavelength: NA	Diabetes (based on FPG >126 mg/dL or taking medications)	Any exposure to light during the night-time was associated with diabetes risk (OR, 2.0; 95% CI, 1.19–3.43) Non- (reference), low- (OR, 1.87; 95% CI, 1.01–3.45), high-LAN (OR, 2.15; 95% CI, 1.17–3.97; *P*=0.014)	Age, sex, race, season
Mason et al. (2022) [41]	Parallel-group study	Healthy young adults (mean age, 26) *n*=20 (men: 30%)	Method: exposure to ALAN (overhead ceiling light bulb) Intensity: BL (100 lux) vs. DL (<3 lux) Exposure: 1-day Time: during sleep (8-hr) Wavelength: NA	HOMA-IR Insulin AUC	Higher HOMA-IR, poorer sleep quality, higher HR with lower HR variability, higher sympathovagal balance associated with higher 30-min insulin AUC (increased insulin resistance the following morning) under the ALAN condition: mainly by increased SNS activation	NA
Grimaldi et al. (2021) [42] -abstract-	Randomized parallel cross-over study	Healthy adults (18–40 years old) *n*=20	Method: light exposure Intensity: BL (100 lux) during sleep vs. dark (<3 lux) Exposure: 1-day Time: overnight Wavelength: NA	Postprandial insulin AUC (OGTT)	Higher insulin AUC under DL than BL condition (*P*=0.029) Higher HR in DL condition was positively correlated with insulin AUC	NA
Albreiki et al. (2017) [43]	Two-way cross-over design study	Healthy adults (mean age, 22) *n*=17 (men: 52.9%)	Method: exposure to ALAN Intensity: BL (>500 lux) vs. DL (<5 lux, reference) Exposure: 1-day Time: between evening and night (6:00 PM–6:00 AM, 12-hr) Wavelength: fluorescent light	Plasma glucose, insulin, HOMA-IR	The total AUC of glucose and insulin levels during the study period was higher in BL than in the DL condition. HOMA-IR levels before and after dinner were comparable between BL and DL condition	Age, BMI
Cheung et al. (2016) [44]	Randomized parallel-group study	healthy adults (20–39 years old; median age, 28) *n*=19 (men: 42.1%)	Method: exposure to ALAN in the morning or evening Intensity: morning or evening BL (260 lux) vs. DL (<5 lux, reference) Exposure: 1-day Time: morning (0.5-hr after awake) or evening (10.5-hr after awake) for 3-hr Wavelength: blue-enriched light (LED)	Plasma glucose, insulin, HOMA-IR	BL exposure in the evening: higher peak glucose and HOMA-IR AUC compared to DL BL exposure in the morning: higher HOMA-IR but no differences in glucose level compared to DL The evening exposure group had higher peak glucose than the morning exposure group	NA

(*Continued to the next page*)

Table 1. Continued

Study	Setting	Population demographics	Type of ALAN exposure	Assessment of diabetes outcomes	Main results and conclusions	Confounding factors
Chamorro et al. (2021) [45]	Randomize, controlled, cross-over experimental study	Normal-weight adults (mean age, 23.4) $n=20$	Method: portable LED lamp exposure Intensity: DL (<5 lux) vs. total darkness (reference) Exposure: 2 consecutive nights Time: night (during 8-hr of sleep) Wavelength: LED	Glucose, insulin, C-peptide	No significant differences in morning levels of glucose, insulin, C-peptide, and HOMA-IR between the two groups	NA

ALAN, artificial light at night; DMSP, Department of Defense's Defense Meteorological Satellite Program; NA, not applicable; FPG, fasting plasma glucose; 2hPG, 2-hour prandial glucose; HbA1c, glycosylated hemoglobin; LAN, light at night; PR, prevalence ratio; CI, confidence interval; BMI, body mass index; ICD-10, International Classification of Diseases 10th edition; HR, hazard ratio; T2DM, type 2 diabetes mellitus; PRS, polygenic risk score; NTLI, night-time light intensity; OR, odds ratio; FU, follow-up; IRR, incident rate ratio; HOMA-IR, homeostatic model assessment of insulin resistance; CM, cardiometabolic; HR, heart rate; BL, blight light; DL, dim light; AUC, area under the curve; SNS, sympathetic nervous system; OGTT, oral glucose tolerance test; LED, light-emitting diode.

1.28; 95% confidence interval [CI], 1.03 to 1.06) [29]. Also, there was a monotonically increasing association between outdoor LAN exposure (continuous variables) and glucose levels (glycosylated hemoglobin [HbA1c], fasting, and 2-hour postprandial glucose) in a dose-dependent manner [29]. However, another cross-sectional study from South India reported a positive relationship of night-time light intensity, a proxy for urbanization, with systolic blood pressure and body mass index but not with fasting plasma glucose [31]. It is important to consider variations in study methods when interpreting different results, as studies may differ in their study population, inclusion criteria, confounding factors included in statistical models, and units used for measuring outdoor ALAN (log-scaled continuous variables [illuminance] vs. nW cm^{-2} sr^{-1} [radiance]). Additionally, it is essential to note that when outdoor ALAN intensity reaches a certain threshold (approximately >20 nW cm^{-2} sr^{-1}), the relationship of ALAN intensity with various glucose metabolism, including insulin resistance markers [29], and incident T2DM risk [30] appears to reach a plateau.

A recent prospective cohort study demonstrated that among the middle-aged United Kingdom (UK) population (mean 55.9 years old), the highest exposure to outdoor ALAN was independently associated with an increased risk of T2DM compared with the lowest exposure (hazard ratio [HR], 1.14; 95% CI, 1.02 to 1.27) [30], with adjusting for environmental confounding factors (air pollution, noise at night). Even though this was the first population-based cohort study investigating the association between outdoor ALAN and diabetes, further evidence in various regions might be required to generalize the association in the global aspect.

Indoor ALAN

Individuals in modern society may spend most of their time indoors [32]. Indoor ALAN is more significant than outdoor ALAN in personal exposure to light pollution [33]. Extensive use of devise-specific screens is associated with poorer perceived dietary choices, lower dietary quality, and negative health-related impact [34]. The extent of indoor ALAN exposure was assessed through self-reported questionnaires, interviews, or photo-meters [35]. While studies investigating the relationship between indoor ALAN and T2DM risk have typically involved smaller study populations than those examining outdoor ALAN, they could help mitigate the ecological fallacy.

Epidemiologic evidence

Exposure to indoor ALAN was generally associated with impaired glucose metabolism and increased T2DM risk across studies. However, there were differences in study design, population, defining ALAN with exposure duration, and outcomes (Table 1). Regarding the association between indoor ALAN and T2DM, ALAN exposure was measured using a portable light meter [36-39], actigraphy [40], or under experimental conditions that were exposed to a certain light intensity [41-45]. A portable light meter was employed as a common tool for objective measurement, often attached to the bed, facing up the ceiling at eye level, to capture night-time exposure [36-38]. In the cross-sectional study conducted among elderly subjects, the prevalent T2DM was positively associated with exposure to indoor ALAN (median, 25 lux) for 2 consecutive evenings (OR, 1.72; 95% CI, 1.12 to 2.64) [36] or for 7 days during sleep (OR, 2.0; 95% CI, 1.19 to 3.43) [40], compared to non-exposures. Furthermore, both studies demonstrated an increase in T2DM prevalence correlating with the increasing intensity of indoor ALAN in a dose-dependent manner [36,40]. Based on findings from a prospective cohort study focusing on the elderly population (aged ≥60 years) with a median follow-up duration of 42 months, 2 consecutive days of exposure to higher indoor bedtime LAN (average ≥5 lux) was associated with a higher risk of developing T2DM compared to dark condition (<5 lux; incident rate ratio, 3.19; 95% CI, 1.38 to 7.47) [37]. Recently, a population-based UK cohort study demonstrated a dose-dependent relationship that brighter light at night for 1 week was associated with a higher risk of T2DM (HR, 1.53; 95% CI, 1.32 to 1.77) even after adjusting for lifestyle factors (diet, physical activity, and sleep duration) [39]. The intensity of ALAN was assessed by calculating average illuminance [36,38,40] or categorization [37,39] through 2 [36,37] or 7 consecutive days [38-40] of exposure. In statistical analysis, sleep components (time to bed and waking time) were adjusted for analysis in the prospective cohort study [37,39] but not in the cross-sectional study [36,40].

The association between indoor ALAN and abnormal glucose metabolism was assessed through a cohort study [38] or randomized parallel cross-over study [41-46] designs. According to 1-year follow-up cohort study conducted among young Chinese adults (16 to 22 years old), any exposure to night-time exposure to indoor ALAN was associated with increased cardiometabolic risk score (the sum of scores of waist circumference, blood pressure, lipid profile, and homeostatic model assessment of insulin resistance [HOMA-IR]; β=1.47; 95% CI, 0.69 to 2.25) [38]. Additionally, regarding the timing of ALAN exposure, the study found that exposure occurring within 1 to 4 hours after sleep onset exhibited a significant association with insulin resistance [38]. According to cross-over studies, the impact of ALAN on glucose metabolism was observed even after a single day of exposure. One-day exposure to bright light (100 lux) at night among healthy young adults demonstrated a higher insulin resistance (defined by postprandial insulin area under the curve) [41,42] with increased heart rate (sympathovagal tone) [41] compared to dim light (<3 lux) exposure. Other studies showed that exposure to more blight light (>500 lux) through evening and night (6:00 PM to 6:00 AM, 12 hours) [43] or to blight light (260 lux) in the evening (3 hours) [44] was associated with higher postprandial glucose levels than exposure to dim light (<5 lux). In addition, glucose intolerance induced by blight light at night manifested early within 30 minutes of exposure [44]. Otherwise, low intensity of dim light at night might not affect glucose metabolism. Two consecutive exposures to dim light (<5 lux) within 1 to 4 hours after sleep onset negatively affected sleep quality but were not associated with altered glucose or insulin resistance levels on the following day compared to total darkness condition [45].

POTENTIAL BIOLOGICAL MECHANISMS BETWEEN ALAN AND GLUCOSE METABOLISM

Circadian rhythm is organized in a hierarchical manner, with a central pacemaker in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [47]. At the molecular level, the circadian rhythm is driven by an auto-regulatory feedback loop of transcription-translation activations and repressors [47]. A heterodimer of transcription factors consisting of the brain and muscle arnt-like protein 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK) induces transcription of period (PER) genes. Upon reaching critical levels, PER represses the transcription process with negative feedback, completing a full circadian cycle of 24 hours [48]. Meanwhile, exposure to ALAN rapidly induces the transcription of PER, which, in turn, disrupts the normal feedback loop. This disruption can phase advance or delay the circadian clock depending on the timing, duration, and intensity of the light signal [49]. Such alternations in the circadian regulatory loops may lead to misalignment between the internal biological clock and external

environmental cues, contributing to metabolic dysregulation.

SCN also regulates the physiological diurnal circadian rhythm that synchronizes central with peripheral clocks in peripheral tissues (muscle, fat, and liver) by communicating neural and humoral signals such as melatonin [50]. Melatonin rhythmicity is considered an indicator of the central circadian rhythms [51], including sleep-wake cycles and metabolism [52]. Melatonin, naturally secreted throughout the day in a rhythmic/diurnal pattern, begins to rise several hours before sleep onset, reaching peak levels during sleep and gradually declining thereafter to maintain low levels throughout the rest of the day [53]. Exposure to ALAN disrupts the circadian rhythm by suppressing melatonin secretion from SCN [54]. Melatonin suppression is the principal putative mechanism mediating environmental exposure at the molecular level by eliciting aberrant epigenetic modifications [55], resulting in β-cell dysfunction and the pathogenesis of diabetes [56]. Conversely, systematic reviews and meta-analyses have shown that melatonin supplements, particularly at higher doses, can reduce fasting blood glucose, HbA1c, and insulin resistance compared to placebo in patients with T2DM [57]. Similar beneficial effects of melatonin supplements on glycemic control and insulin sensitivity have been observed in patients with T2DM undergoing hemodialysis [58].

Circadian disruption desynchronizes the central and peripheral biological clock, resulting in postprandial hyperglycemia induced by peripheral organ insulin resistance [42,43]. This contributes to increased hepatic endogenous glucose production [9], β-cell dysfunction [59-61], and a desynchronized sympathetic nerve system [42,62]. In addition, through non-SCN neural sympathetic pathways, exposure to ALAN blocks adaptive thermogenesis in brown adipose tissue, resulting in impaired glucose tolerance [63].

KNOWLEDGE GAPS ABOUT THE RELATIONSHIP BETWEEN ALAN AND T2DM

Components of ALAN

Intensity and duration of ALAN exposure

An experimental study has demonstrated that the impact of ALAN on glucose metabolism is influenced by the intensity and duration of exposure [64]. Dose-dependent relationships between ALAN intensity (measured as the luminous flux per unit area, in lux) and impaired glucose metabolism have been well documented in both epidemiological [30,37,39,40] and experimental studies [41,45,46]. However, there remains a lack of consensus on specific cut-off values for safe exposure levels.

Diabetes risk has been found to be related to varying durations of exposure to ALAN, ranging from 2 days [36,37] to 7 days [38-40]. A study from Finland demonstrated that the risk of sleep problems increased with longer durations of living in an area with intense light exposure, from 2 months to more than a year [65]. Additionally, the risk of incident T2DM among shift workers increased as the number of night shifts worked per month increased [17]. In contrast, under the experimental conditions involving exposure to a computer screen for 2 hours before sleep for up to 6 days, deleterious effects on sleep health occurred within the first day of exposure without cumulative effects [66]. Moreover, prior exposure to ALAN has been found to attenuate melatonin suppression in response to subsequent light exposure [67]. Despite these findings, there is still a paucity of research on whether the duration of ALAN exposure affects glucose metabolism more significantly.

Source (wavelength) of ALAN and individual sensitivity to ALAN

The specific wavelength of ALAN and individual variations in light sensitivity play a crucial role, with different wavelengths of light exposure having varying effects on glucose metabolism [64]. Due to the heightened sensitivity of retinal ganglion cells to short-wavelength (400 to 500 nm) blue-light waves [68,69], the adoption of solid-state LED has the potential to exacerbate light pollution and disrupt circadian rhythmicity [70]. Blue-enriched light has been associated with increased insulin resistance and higher glucose levels in the evening [44], whereas blocking blue light can improve insulin resistance, reduce blood glucose levels [71], and enhance sleep quality [72].

Notably, illuminance levels derived from melanopsin, known as melanopsin equivalent daylight illuminance (EDI), do not align with the conventional units of light brightness (lux) typically utilized in practical settings. Melatonin production is affected by the amount of light detected by light-sensitive melanopsin, independent of visual factors like color or glare [73]. Expert consensus-based recommendations suggest that optimal melanoptic EDI should be below 10 lux at the eye level (approximately 1.2 m in height) in the evening, and below 1 lux during the night-time [74]. Generally, units of melanoptic EDI (lux) are lower than those of light brightness (lux). However, melanoptic EDI can be higher under specific light conditions

such as color temperature, LED-type lights, and shorter wavelengths, even at the same photopic illuminance level [74]. Furthermore, there is considerable variability in the average melanoptic illuminance across different lighting sources, with a range spanning 20-fold [75].

The response to light can vary according to age [75], individual sensitivity to light, and home lighting sources, such as incandescent and LED lights [76]. Additionally, individual light sensitivity shows even greater diversity, exceeding 50-fold under identical light exposure conditions [75]. These factors pose significant challenges in accurately predicting the effects of indoor ALAN on the circadian system [76]. To date, studies investigating the association between ALAN exposure and T2DM risk have primarily focused on elderly individuals aged more than 60 [36,37,40] or young healthy adults in their 20s [38,41,43-45]. Future studies encompassing a broader age range are essential, as the response to light exposure and consequent melatonin suppression attenuated with age [77,78]. Given these age-related differences in light sensitivity, there remains a dearth of evidence regarding the impact of various forms of light exposure, including light sources, wavelength, and individual sensitivity, on metabolic outcomes in other age groups.

Timing of ALAN exposure

The timing of ALAN exposure is another factor that can impact glucose metabolism [64]. The timing of light exposure throughout the day affects the 24-hour melatonin profile. Studies investigating the association with glucose metabolism have adopted various time frames for ALAN exposure, including (1) evening hours until bedtime [36,44]; (2) the period from bedtime to awakening [37,38,40-42,45]; and (3) from evening until the following morning [43]. Evening light delays melatonin secretion [79] and impairs glucose tolerance by reducing late-phase insulin sensitivity [80]. Conversely, daytime light can augment nocturnal melatonin secretion, reduce the melatonin suppression effect in response to late evening or night-time light exposures [52,63], diminish subjective sleepiness, and enhance performance [81]. In contrast to nocturnal light exposure, evening light (at least 3 hours before bedtime) has improved sleep-related outcomes and work performance [82]. Additionally, studies have indicated that the influence of light exposure on both melatonin suppression and glucose metabolism is more prominently affected by the initial hour of exposure rather than the overall duration of exposure [83,84]. Further research is needed to determine the optimal exposure timing and patterns for metabolic outcomes, including T2DM.

Disparities in the burden of ALAN exposure

Conditions that were vulnerable to ALAN exposure could be different according to race/ethnicity and socioeconomic status. Individuals in rural areas or with minoritized backgrounds have generally been shown to be more exposed to ALAN compared to their counterparts [85]. In addition, the association between exposure to indoor ALAN and poor sleep health was the most significant in non-Hispanic Blacks than in non-Hispanic Whites among US women [86]. However, evidence was sparse on whether there were differences or disparities in exposure burden to ALAN and relation to T2DM risk by gender, race/ethnicity, or other socioeconomic factors. Otherwise, to date, the evidence of a relationship between ALAN and impaired glucose metabolism documented through a population-based study was confined to Asia [31,36,37], the UK [30,39], and the USA [40]. Considering pervasive exposure to ALAN across the globe, more population-based studies conducted in various regions are essential to understand the impact of ALAN on T2DM risk and to generalize it.

POTENTIAL ROLE OF SLEEP HEALTH AND OTHER LIFESTYLE FACTORS (PHYSICAL ACTIVITY AND DIETARY PATTERNS) IN THE ASSOCIATION BETWEEN ALAN AND T2DM

Sleep health

Sleep health is closely related to ALAN exposure and subsequently associated with T2DM risk. Exposure to indoor or outdoor ALAN has been associated with insufficient sleep duration [87,88], being prominent in indoor ALAN settings compared to outdoor ALAN exposure [88]. For example, indoor ALAN exposure (e.g., television) was associated with self-reported multiple-dimensional sleeping problems such as sleep deprivation, insomnia, and difficulty falling and staying asleep among US women [86]. Engaging with a smartphone before bedtime is one of the prevailing sources of illumination during night-time in contemporary times. Primarily, using blue-light LED smartphones at night negatively affects sleep and commission errors [89]. In addition, under exposure to ALAN at bedtime, individuals experience poorer sleep quality and exhibit a higher sympathovagal tone, concomitant with elevated

insulin resistance [41].

Regarding the association between sleep components and T2DM risk, poor sleep health, characterized by shorter sleep duration, frequent napping, and poor sleep quality, is associated with an increased risk of T2DM [90-92] and inadequate glycemic control in patients with T2DM [93]. Also, sleep deprivation was associated with increased insulin resistance the following morning, as evidenced by a 30% rise in HOMA-IR after a single-day exposure to blue-enriched light [44] and a 50% to 65% elevation following consecutive 3-day sleep restriction compared to a fully rested state [94].

Exposure to ALAN, sleep disturbance, and related factors such as shift work or evening chronotype are intricately interrelated. The association between ALAN exposure, sleep health, and T2DM risk may be mediated by disrupted circadian rhythm. Sleep loss and shift work are jointly associated with the risk of T2DM [95]. Moreover, the increase in insulin resistance following sleep loss and circadian misalignment was nearly twice as significant as following sleep loss alone under aligned conditions (58% vs. 32%) [96]. On the contrary, the impact of sleep loss on impaired glucose metabolism was observed only when accompanied by circadian disruption [97]. The experimental study also showed that augmented insulin resistance and inflammation markers under shift work were primarily derived from circadian misalignment, irrespective of sleep deprivation [98].

The exposure to ALAN might be independently associated with T2DM risk even after adjustment for concurrent shift work [30] or sleep components (total sleep time and sleep efficiency) [37]. Moreover, elevated postprandial levels of insulin and glucagon-like peptide-1, coupled with increased insulin resistance resulting from sleep deprivation and exposure to nighttime light, were not evident under conditions of sleep deprivation in darkness [99]. Therefore, when analyzing the association between ALAN exposure and sleep with T2DM risk, it is essential to consider not only sleep *per se* but also its impact on circadian rhythm as a potentially critical factor in the association between ALAN and glucose metabolism [47].

Physical activity and dietary patterns

Physical activity and dietary patterns are important factors to consider when evaluating the relationship between ALAN and T2DM. Circadian rhythm, a major regulator of metabolism, is entrained by various external cues (zeitgebers) such as light, food intake, physical activity, and social interaction [100]. ALAN exposure is associated with sleep disturbances, which can, in turn, affect physical activity and dietary patterns. Conditions such as shift work or electronic device use that expose individuals to ALAN have been associated with increased sedentary behavior [101] and decreased opportunities for physical activity [102]. Additionally, the timing of food intake, a critical factor in energy metabolism, is often delayed under ALAN exposure, leading to a higher risk of obesity even with similar total daily caloric intake, as shown in both mice [103] and human studies [104,105].

However, the relationship between ALAN and lifestyle factors is complex. For instance, one experimental study found that voluntary exercise could attenuate the metabolic effects of dim ALAN without altering circadian rhythms [106]. Moreover, previous studies have demonstrated that the association between ALAN and T2DM or insulin resistance remained significant even after adjusting for physical activity [37,38] or food addiction [38]. This suggests that ALAN may have an independent effect on metabolic health, beyond its influence on physical activity and dietary patterns. While physical activity and dietary habits may mediate the association between ALAN and T2DM [107,108], further research is needed to disentangle the complex interplay between these factors and determine the extent to which ALAN independently influences metabolic health, regardless of lifestyle modifications.

POTENTIAL ASSOCIATION BETWEEN ALAN AND DIABETES MANAGEMENT: IMPLICATIONS FOR CHRONOTHERAPY, CHRONONUTRITION, AND PHARMACOLOGICAL TREATMENT

Evidence remains limited regarding the role of ALAN in non-pharmacological/pharmacological treatment and management strategies for patients with T2DM. Given the diurnal physiologic rhythm of insulin secretion and sensitivity, which peaks at waking and reaches nadirs during sleep [109], the desynchronization of central and peripheral clocks induced by ALAN has been linked to the stimulation of hepatic glucose production, potentially contributing to morning fasting hyperglycemia [110]. Furthermore, ALAN exposure has been demonstrated to exacerbate the dawn phenomenon, characterized by early morning fasting hyperglycemia without nocturnal hypoglycemia, by extending hyperglycemia into the post-breakfast period [111].

Concerning the timing of light exposure throughout the day, a previous study showed that, in patients with T2DM, even morning exposure to bright light is associated with increased sympathetic tone, impaired β-cell insulin sensitivity, and decreased satiety after meals, leading to fasting and prandial hyperglycemia compared to dim light exposure [112]. Alternatively, optimizing indoor lighting to more closely resemble natural light/dark cycles has been shown to promote favorable metabolic conditions, increase energy expenditure following dinner, and conserve metabolic rate during sleep, compared to exposure to bright evening light (1,250 lux) [46].

Orexin, neuropeptides generated in the hypothalamus, plays a crucial role in regulating the sleep/wake cycle and energy homeostasis [113]. Orexin neurons are influenced by signals that regulate the sleep cycle, autonomic tone, and circadian rhythms [114]. Experimental studies have shown that intracerebroventricular administration of orexin antagonist can prevent endogenous hyperglycemia at the end of the sleep period [115], indicating that orexin interplays with circadian rhythms to control the daily glucose metabolism. Consequently, chrononutrition interventions, which aim to synchronize food intake with both dietary quality and circadian rhythm, have emerged as a potential strategy for managing diabetes [116]. In addition, personalized nutrition therapy is being developed based on individual epigenetic and genetic patterns, gut microbial composition, and circadian rhythm, incorporating chrononutrition principles [117,118]. However, more research is essential to establish robust conclusions and provide evidence-based recommendations for applying this strategy concept in treating T2DM.

In terms of pharmacological treatment, even though the evidence is still lacking, chronotherapy that consists of optimized circadian rhythm and regulating the timing of drug medications has emerged in various conditions to achieve more treatment efficacy and fewer side effects [119,120]. For example, the experimental studies demonstrated the time-dependent effects of metformin on blood glucose and its interaction with the circadian rhythm [121]. Accordingly, future research is needed to investigate the impact of ALAN on diabetes medication strategies in patients with T2DM through clinical trials, considering that both are influenced by circadian rhythm.

Beyond the direct association discussed previously, we propose a possible clinical implication where exposure to ALAN may additionally influence T2DM management in patients with T2DM through interactions with chronotype and eating behaviors (Fig. 1). Individuals characterized by evening chronotypes [122], exposure to ALAN [123], and poor sleep quali-

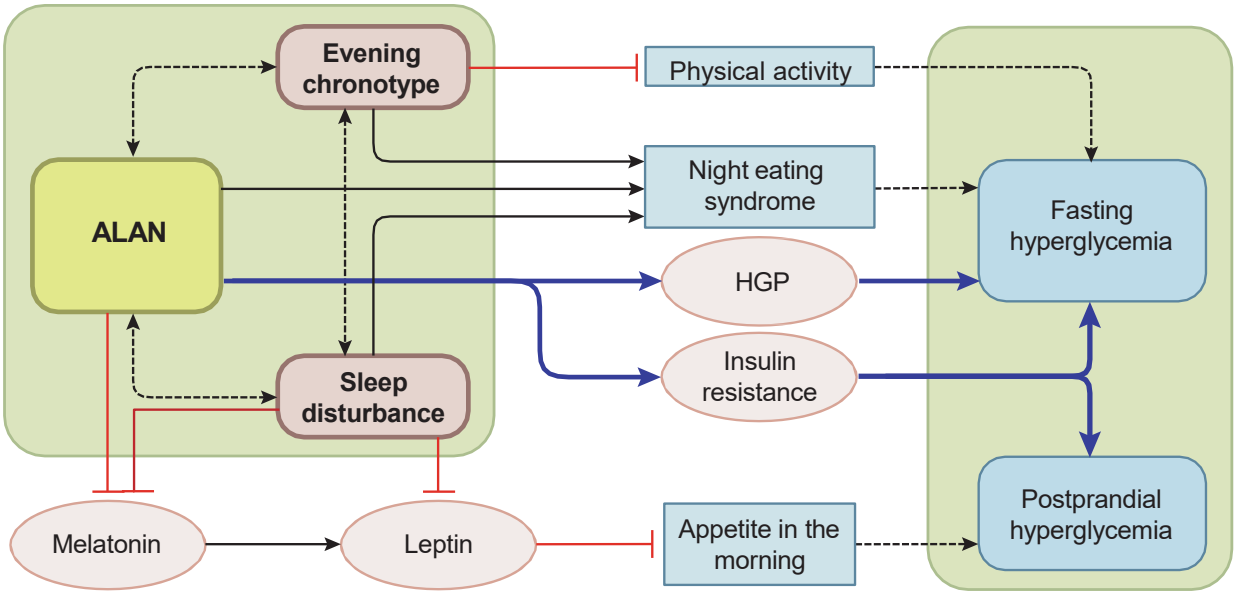

Fig. 1. Possible clinical pathway: artificial light at night (ALAN), sleep disturbance, evening chronotype, and abnormal glucose metabolism in patients with type 2 diabetes mellitus. The black arrows denote the direction of the pathway. T-bars indicate the suppression of the following pathway. The dotted arrows represent possible bidirectional pathways between two components. HGP, hepatic glucose production.

ty [124] are more likely to exhibit delayed dinner times and engage in unhealthy eating behaviors, potentially due to their shifted sleep-wake patterns. Having dinner later has been associated with both impaired glucose tolerance [84] and increased T2DM risk [85] compared to earlier dinner times. An experimental study demonstrated that exposure to ALAN is associated with obesity, potentially due to a shift in the timing of food intake, even when caloric intake and total daily activity remain constant [103]. Additionally, individuals with an evening chronotype are known to have a higher prevalence of night-eating syndrome [125]. This syndrome is characterized by habitually consuming at least 25% of daily calories after dinner, experiencing frequent cravings for food after dinner or during the night, and believing that eating is necessary to fall asleep. Furthermore, individuals with an evening chronotype tend to experience lower sleep quality, higher levels of chronic work-related fatigue, and reduced exposure to adequate light levels during their waking hours compared to those with an early chronotype [126,127]. Also, both exposure to ALAN and sleep deprivation suppress melatonin production, leading to decreased leptin levels, a satiety hormone [125,128]. This reduction in leptin is associated with elevated sympathovagal tone and a heightened appetite in the morning [129]. These findings highlight the potential importance of incorporating ALAN exposure and related lifestyle factors, such as chronotype or eating behaviors, into managing patients with T2DM. However, the current evidence remains limited, necessitating further research to elucidate the impact of ALAN exposure and related conditions on management and treatment strategies for patients with T2DM.

CONCLUSIONS

The ubiquity of ALAN or light pollution, often driven by lifestyle changes, poses a significant challenge due to its potential to disrupt circadian rhythms. Even though it has been established that ALAN exposure has a significant association with abnormal glucose metabolism and T2DM risk, comprehensive research considering various types and patterns of exposure to ALAN with the extent and sensitivity of melatonin suppression by ALAN is essential to establish ALAN as a potential factor for prevention and management of diabetes. Furthermore, various demographic conditions and socioeconomic factors related to ALAN exposure should be incorporated to assess the association between ALAN and T2DM. Also, even though there appears to be a trend of abnormal glucose metabolism and increasing T2DM risk with exposure intensity up to a certain threshold, there is still no established cut-off value for safe ALAN exposure to be concluded.

In patients with T2DM, circadian disruption caused by ALAN exposure, poor sleep health, and evening chronotype are closely interrelated. These complex components can potentially influence individuals' physical activity, alertness, daily eating patterns, and even diurnal glucose profiles. Although further studies are still required to bridge the knowledge gap, chrononutrition and chronotherapy integrating ALAN exposure are expected to serve as emerging critical strategies in developing individualized therapeutic approaches for diabetes prevention and management.

CONFLICTS OF INTEREST

Yong-Moon Mark Park has been statistical advisors of the *Diabetes & Metabolism Journal* since 2011. He was not involved in the review process of this article. Otherwise, there was no conflict of interest.

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